Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

21 July 2020

DEPARTMENT MEMORANDUM
No. 2020- 0381

TO : **ALL UNDERSECRETARIES AND ASSISTANT SECRETARIES DIRECTORS OF BUREAUS, SERVICES AND CENTERS FOR HEALTH DEVELOPMENT; MINISTER OF HEALTH — BANGSAMORO AUTONOMOUS REGION IN MUSLIM MINDANAO; EXECUTIVE DIRECTORS OF SPECIALTY HOSPITALS AND NATIONAL NUTRITION COUNCIL; CHIEFS OF MEDICAL CENTERS, HOSPITALS, SANITARIA AND INSTITUTES AND ALL OFFICES INVOLVED**

SUBJECT : **Interim Guidelines on the COVID-19 Disease Severity Classification and Management**

I. BACKGROUND

As the number of Coronavirus Disease 2019 (COVID-19) cases continue to rise, appropriate clinical management for the different disease severity of COVID-19 must be undertaken. This is to ensure fast recovery and to reduce mortality.

Based on the initial and current Philippine Society for Microbiology and Infectious Diseases (PSMID) and Pediatric Infectious Disease Society of the Philippines (PIDSP) Clinical Practice Guidelines (CPG) for COVID-19, patients are evaluated for their disease severity as either mild, severe or critical for triaging and referral purposes. Adult patients were also initially classified clinically as follows for management purposes:

1. Adults (age<60) with stable or no comorbid diseases and uncomplicated upper respiratory tract infection
2. Adults (age >60) with stable or unstable comorbid diseases and pneumonia
3. Adults with severe pneumonia, severe sepsis or septic shock
4. Adults with Acute Respiratory Distress Syndrome

On the other hand, pediatric patients were classified as:

1. Suspect COVID-19 case with Severe/Critical symptoms
2. Suspect COVID-19 case with Non-severe symptoms which may range from Mild to Moderate symptoms
3. Probable COVID-19 case
4. Confirmed COVID-19 case

As the situation has evolved and new knowledge and information became available, COVID-19 disease severity classification and corresponding definitions were also updated. The new World Health Organization (WHO) disease severity classification includes **mild, moderate, severe and critical diseases**. This classification is being used both for referral and management purposes.

These guidelines are hereby issued to guide the health facilities and other disease reporting units on the updated definitions of COVID-19 disease severity classification based on WHO Clinical Management of COVID-19 27 May 2020 and the PSMID Clinical Practice Guidelines as of July 20, 2020.

II. DISEASE SEVERITY CLASSIFICATION OF PATIENTS WITH PROBABLE OR CONFIRMED COVID-19

A. Mild Disease

1. Symptomatic patients presenting with fever, cough, fatigue, anorexia, myalgias; other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting; loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms with NO signs of pneumonia or hypoxia

B. Moderate Disease

1. Adolescent or adult with clinical signs of non-severe pneumonia (e.g. fever, cough, dyspnea, respiratory rate (RR) = 21-30 breaths/minute, peripheral capillary oxygen saturation (SpO2) >92% on room air)
2. Child with clinical signs of non-severe pneumonia (cough or difficulty breathing and fast breathing [< 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40] and/or chest indrawing)

C. Severe Disease

1. Adolescent or adult with clinical signs of severe pneumonia or severe acute respiratory infection as follows: fever, cough, dyspnea, RR>30 breaths/minute, severe respiratory distress or SpO2 ≤ 92% on room air
2. Child with clinical signs of pneumonia (cough or difficulty in breathing) plus at least one of the following:
    a. Central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.
    b. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40.

D. Critical Disease - Patients manifesting with acute respiratory distress syndrome, sepsis and/or septic shock

1. **Acute Respiratory Distress Syndrome (ARDS)**
    a. Patients with onset within 1 week of known clinical insult (pneumonia) or new or worsening respiratory symptoms, progressing infiltrates on chest X-ray or chest CT scan, with respiratory failure not fully explained by cardiac failure or fluid overload
2. **Sepsis**
    a. Adults with life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of

coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia

b. Children with suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome criteria (abnormal temperature [> 38.5 °C or < 36 °C]; tachycardia for age or bradycardia for age if < 1 year; tachypnea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands), of which one must be abnormal temperature or white blood cell count.

3. **Septic Shock**

a. Adults with persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level >2 mmol/L

b. Children with any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.

III. IMPLEMENTING GUIDELINES

A. All health facilities and other disease reporting units shall follow the definitions above. The reporting mechanism of the disease severity will be detailed in a separate issuance.

B. After initial assessment, management and stabilization, patients shall be referred to the appropriate COVID-19 care destination: within the health facility (critical care unit or ward), to a different health facility, temporary treatment and monitoring facility or home, according to patient medical needs and established COVID-19 care pathways. Patient care pathway for each disease severity classification shall follow the Algorithm For COVID-19 Referral and Triage (**See Annex A**) as adopted in the PSMID Clinical Practice Guidelines as of July 20, 2020.

C. Patients with mild illness may not require emergency interventions or hospitalization; however, patients with moderate, severe or critical illness should be admitted in a hospital. Isolation is necessary for all suspect, probable or confirmed cases regardless of severity to contain virus transmission.

D. Some patients develop severe pneumonia and require oxygen therapy, and a minority progress to critical disease with complications such as respiratory failure or septic shock.

E. Early identification of severe disease shall be ensured to allow rapid initiation of optimized supportive care treatments and safe, rapid referral to a designated COVID-19 referral hospital (with access to oxygen and respiratory support).

F. Known risk factors for rapid deterioration, severe disease, and/or increased mortality are: older age (> 60 years) and non-communicable diseases such as cardiovascular disease, diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease. Patients with one or more of these risk factors should be monitored closely for deterioration.

G. Detailed clinical management for each COVID-19 disease severity classification shall follow the current local clinical practice guidelines by the Philippine Society for Microbiology and Infectious Diseases (**See Annex B**).

H. Health care provider networks faced with limited range of service capabilities and absorptive capacities, may adopt localized service allocation across all public and private health care providers; provided that, (a) the goal of ensuring that the right patient is given the right service at the right time is achieved; (b) with a plan to continually expand network-wide service capability is in place; and (c) in consideration of equitable access to health service, and capability of provider to deliver the appropriate service. In this endeavor, local government units, in coordination with their respective DOH Centers for Health Development, are highly encouraged to engage all public and private institutional and non-institutional providers and agree on their respective service level allocation, with corresponding agreements and referral arrangements for both individual-based and population-based health services, as necessary.

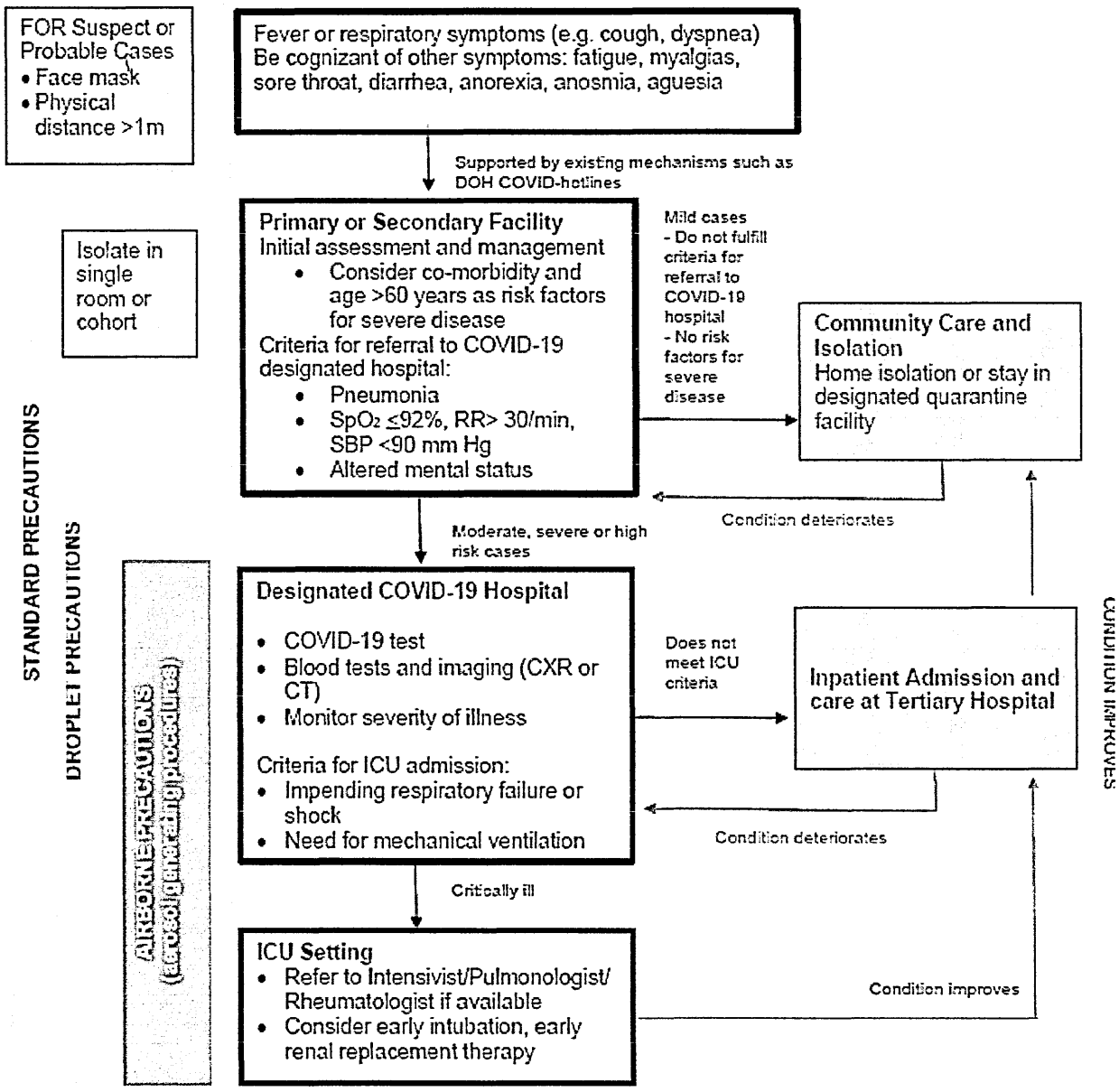
IV. REPEALING CLAUSE

Department Memorandum 2020-0138 entitled "Adoption of PSMID Clinical Practice Guidelines on COVID-19" and other related issuances inconsistent or contrary to the provisions of this Memorandum are hereby repealed.

For strict compliance.

FRANCISCO T. DUQUE III, MD, MSc
Secretary of Health

Annex A. Algorithm for COVID-19 Referral and Triage (*PSMID Guidelines as of July 20, 2020*)



^Modified from WHO Algorithm for COVID-19 Referral and Triage

"ANNEX B"

Philippine Society for Microbiology and Infectious Diseases
Philippine College of Chest Physicians
Philippine College of Physicians
Philippine Rheumatology Association
Philippine College of Hematology and Transfusion Medicine

INTERIM GUIDANCE ON THE CLINICAL MANAGEMENT OF ADULT PATIENTS WITH SUSPECTED OR CONFIRMED COVID-19 INFECTION

Version 3.1, as of July 20, 2020

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TABLE OF ACRONYMS

CAP – Community Acquired Pneumonia

COVID-19 – Coronavirus disease 2019

NPS – Nasopharyngeal swab

OPS - Oropharyngeal swab

PUI- Person Under Investigation

PUM – Person Under Monitoring

SARS CoV2 - Severe Acute Respiratory Syndrome Coronavirus -2

ARDS- Acute Respiratory Distress Syndrome

BACKGROUND

The novel coronavirus, SARS CoV-2, first isolated in Wuhan City, Hubei province, in China last December 2019, has caused a global pandemic with staggering speed. As of June 30, 2020, there were more than > 10,000,000 COVID-19 cases worldwide, with more than 500,000 reported deaths (1).

The situation in the Philippines has also rapidly evolved, with a single case identified last January 30, 2020, to over 200 cases by March 16, 2020. Initial cases were imported from China and other neighboring Asian countries. Sustained community transmission led to the implementation of intensified quarantine measures in March 2020. Cases plateaued in May which led to the relaxation of quarantine measures. However, by mid-June, there has been a resurgence of cases within the National Capital Region and in Cebu. As of July 2020, the country has more than 60,000 reported cases with more than 1,000 deaths(2).

The clinical presentation of COVID-19 disease ranges from a mild common cold-like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Large, retrospective case series from China have shown that the elderly, those with co-morbidities, and those with pneumonia are most at risk for severe disease (3-6). The predominant mode of transmission remains person to person spread via respiratory droplets. The peak of infectiousness is just before or within 5 days of symptom onset. The main driver of transmission remains the symptomatic group although presymptomatics and asymptomatics may transmit the disease but to a lesser extent.

Treatment is largely supportive, although in-vitro and early observational data regarding the off-label use of several re-purposed drugs, such as remdesivir, chloroquine, hydroxychloroquine, lopinavir-ritonavir and tocilizumab showed some promise. Various pharmacologic and non-pharmacologic interventions are being investigated in a clinical trial or given as compassionate use. Supportive care and intensive respiratory management remain the standard of care for COVID-19

This document is an update of the March 31, 2020 guidelines released by the Philippine Society for Microbiology and Infectious Diseases. New evidence have been published since then necessitating this update.This document is written to guide clinicians and health care workers in their COVID-19 related management decisions. It is based on available scientific evidence that is also rapidly evolving, as more is discovered about the pathophysiology of SARS CoV-2 and the pathogenesis of the disease. **As such, the recommendations in this guideline are based on limited, often low-quality evidence, and need to be carefully balanced with clinical judgment.** The use of investigational drugs should be discussed with the patient or a legally authorized representative carefully outlining the potential adverse reactions and the potential clinical benefits of these investigational drugs. A signed informed consent should be obtained by the clinician.

These recommendations will be updated regularly and are subject to change depending on the evolving evidence as more research is done and results get published. Several knowledge gaps remain and we aim to avoid premature recommendations for potentially harmful interventions pending the results of ongoing clinical trials and validation studies. This guidance may not cover all possible scenarios. In such situations, clinical judgment shall take precedence.

SUMMARY OF TREATMENT RECOMMENDATIONS

RECOMMENDATION 1:
For patients with mild COVID-19 disease, supportive care is recommended. These include antipyretics for fever, oral fluids for hydration, isolation at home or in temporary treatment and monitoring facilities. [Strong recommendation, low quality of evidence]

Routine empiric antibiotics and routine anti-influenza drugs are NOT recommended for mild COVID-19 disease. [Strong recommendation, low quality of evidence]

RECOMMENDATION 2:
Remdesivir may be given to hospitalized adult patients with severe COVID-19 in the setting of a clinical trial or under compassionate use, pending the results of ongoing randomized clinical trials and full analysis of completed trials. Dosing regimen of remdesivir is 200 mg IV loading dose on Day 1 followed by 100 mg IV once a day for 5-10 days. [Strong recommendation, low quality of evidence]

There is insufficient evidence to recommend the routine use of remdesivir among hospitalized patients with mild to moderate COVID disease except in the context of a clinical trial.

RECOMMENDATION 3:
Chloroquine (CQ) or hydroxychloroquine (HCQ) as monotherapy or in combination with a macrolide (e.g. azithromycin) or an antiviral agent (lopinavir-ritonavir, favipiravir) among hospitalized patients with probable or confirmed COVID-19 pneumonia is NOT recommended. [Strong recommendation, moderate quality of evidence]

Chloroquine or hydroxychloroquine is not recommended for outpatients with early or mild COVID-19 disease except in the context of a clinical trial.

Chloroquine or hydroxychloroquine is not recommended for prophylaxis or prevention of COVID-19 except in the context of a clinical trial. [Strong recommendation, low quality of evidence]

RECOMMENDATION 4: Lopinavir-ritonavir (LPV/r) as monotherapy or in combination with hydroxychloroquine or other immunomodulators is NOT recommended among hospitalized patients with probable or confirmed COVID-19 pneumonia. [Strong recommendation, moderate quality of evidence]

RECOMMENDATION 5: There is insufficient evidence to recommend the routine use of favipiravir in the treatment of COVID-19 except in the context of a clinical trial or for compassionate use among patients with moderate COVID-19 disease. Clinical trial dosage is 1800 mg 2x/day loading dose then 800 mg 2x/day for 13 days.

RECOMMENDATION 6:
Corticosteroid therapy (dexamethasone) is recommended as adjunctive treatment for COVID-19 patients requiring oxygen support and for patients on mechanical ventilation. The recommended dose for dexamethasone is 6 mg IV for 10 days. [Strong recommendation, moderate quality of evidence]

Corticosteroid therapy (dexamethasone) is not recommended for COVID-19 patients who do not require oxygen support (mild to moderate disease severity). [Strong recommendation, moderate quality of evidence]

Inhaled steroids are NOT recommended for the treatment of COVID-19 pending the results of ongoing studies.

Oral, inhaled or IV steroids are NOT recommended for prophylaxis or prevention of COVID-19.

RECOMMENDATION 7: There is insufficient evidence to recommend the use of tocilizumab and other IL-6 inhibitors for the management of COVID-19 in severe hospitalized patients with suspected cytokine storm except in the context of a clinical trial or for compassionate use.

RECOMMENDATION 8: There is insufficient evidence to support the use of intravenous immunoglobulin (IVIg) for the management of COVID-19 among severe hospitalized patients except in the context of a clinical trial.

RECOMMENDATION 9: There is insufficient evidence to support the use of convalescent plasma (CP) for hospitalized COVID-19 patients except in the context of a clinical trial. CP may be considered for patients with severe COVID-19 under compassionate use or for eligible patients with moderate to severe COVID-19 in institutions where there is an ongoing clinical trial, duly approved by the appropriate corresponding Institutional Regulatory Board.

RECOMMENDATION 10: There is insufficient evidence to support the routine use of interferon (IFN) for patients hospitalized patients with COVID-19 except in the context of a clinical trial or for compassionate use.

RECOMMENDATION 11: There is insufficient evidence to support the routine use of hemoperfusion as adjunctive management for severe COVID-19 patients suspected to have cytokine storm except for compassionate use.

RECOMMENDATION 12: There is insufficient evidence to support the use of vitamin C and zinc as adjunctive treatment for COVID-19.

I. Diagnostic testing

All symptomatic individuals with suspected SARS COV-2 respiratory tract infection should undergo testing for COVID-19 as well as ancillary tests warranted by their clinical condition. Benefits of prompt testing include:

1. Proper allocation of personal protective equipment
2. Prevention of nosocomial spread and subsequent community transmission
3. Guidance in treatment decisions and enrollment in clinical trials

Tests for SARS COV-2 (COVID-19)

A. Real-time reverse transcription-polymerase chain reaction (RT-PCR) assay –

The currently recommended test to confirm COVID-19 infection is an RT-PCR assay, which detects the viral RNA. Using this assay, SARS CoV-2 can be detected in nasal or pharyngeal samples, sputum, bronchoalveolar lavage fluid, and other bodily fluids, including feces and blood.

Several RNA gene targets are used by different manufacturers. Most tests target one or more of the envelope (*env*), nucleocapsid (*N*), spike (*S*), RNA-dependent RNA polymerase (*RdRp*), and *ORF1* genes. Viral RNA is measured by the cycle threshold (Ct) value which becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset. The Ct is the number of replication cycles required to produce a fluorescent signal, with lower Ct values representing higher viral RNA loads. A Ct value less than 40 is clinically reported as PCR positive. The positivity starts to decline by week 3 until it becomes undetectable. See Figure 1. (7)

The sensitivity and specificity of the RT-PCR assay according to the type of specimen and based on a pre-test probability of 10% are summarized in Table 1 (8). Among the upper respiratory tract specimens, nasopharyngeal and nasal swabs had the highest sensitivity. In a study of 1078 specimens collected from 205 patients with confirmed COVID-19 infection, RT-PCR positivity was highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swab (32%), feces (29%) and blood (1%). None of the urine specimens tested positive. The mean cycle threshold values of all specimen types were more than 30 except for nasal swabs with a mean Ct value of 24.3, indicating higher viral loads(9).

Table 1: Sensitivity and Specificity of RT-PCR Based on Type of Sample

	Oral	Nasal	NP	Nasal vs NP	Saliva	Mid-turbinate
Sensitivity % (95% CI)	56 (35-77)	76 (59-94)	97 (92-100)	95 (69-94)	85 (69-94)	100 (93-100)
Specificity % (95% CI)	99 (99-100)	100 (99-100)	100 (99-1 00)	100 (99-100)	100 (99-100)	100 (99-100)

False negative results of RT-PCR assays may be due to inadequate sample and inappropriate timing of sample collection in relation to symptom onset. Over the 4 days of infection before the typical time of symptom onset (day 5), the probability of a false-negative result in an infected person decreased from 100% on day 1 to 68% on day 4. On the day of symptom onset, the median false-negative rate was 38%. This decreased to 20% on day 8 (3 days after symptom onset) then began to increase again, from 21% on day 9 to 66% on day 21. The false-negative rate was minimized 8 days after exposure, 3 days after the onset of symptoms on average.

RECOMMENDATIONS:

- All symptomatic individuals suspected of having COVID-19 patients should undergo SARS CoV-2 RT-PCR assay testing to diagnose COVID-19 infection.
- Nasopharyngeal specimens rather than oropharyngeal or saliva specimens are preferred for swab-based SARS-CoV-2 testing.
- Specimens from sputum, endotracheal aspirates, and bronchoalveolar lavage among hospitalized patients may also be sent directly to the microbiology laboratory for processing.
- The qualitative reporting of results of SARS-COV-2 RT-PCR as positive or negative is sufficient for DIAGNOSIS but may be supplemented by a CYCLE THRESHOLD report, a semi-quantitative value, correlated with timing of symptom onset to guide infection control, public health and occupational health decisions (i.e., duration of isolation, clearance for work, clearance for medical or surgical procedures).

B. Rapid Tests based on Antigen Production – Rapid antigen test detects the presence of viral proteins (antigens) expressed by the COVID-19 virus in a sample from the respiratory tract of a person. If the target antigen is present in sufficient concentrations in the sample, it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visually detectable signal, typically within 30 minutes. The antigen(s) detected are expressed only when the virus is actively replicating; therefore, such tests are best used to identify acute or early infection.

However, several factors affect the performance of the test, including time from onset of illness, the concentration of virus in the specimen, the quality of the specimen collected from a person and how it is processed, and the precise formulation of the reagents in the test kits. Based on antigen-based RDTs for other respiratory diseases such as influenza, the sensitivity of these tests might be expected to vary from 34% to 80%[10].

Half or more of COVID-19 infected patients might be missed by such tests, depending on the group of patients tested. Additionally, false-positive results could occur if the antibodies on the test strip also recognize antigens of viruses other than COVID-19 (e.g. cross-reaction). If any of the commercial antigen detection tests demonstrate adequate performance, they could potentially be used as triage/screening tests to rapidly identify patients who are very likely to have COVID-19, reducing or eliminating the need for expensive molecular confirmatory testing.

The SARS rapid antigen test is a lateral flow immunofluorescent sandwich assay intended for the qualitative detection of the nucleocapsid protein antigen from SARS-

CoV-2 in nasopharyngeal and nasal swab specimens directly or after the swabs have been added to either the universal transport media or viral transport media from individuals who are suspected of COVID-19.

Commercially available rapid antigen tests report a sensitivity of 87% (95% CI 52.9 to 97.8) and a specificity of 100% (95% CI 96.8 to 100) based on a small study using direct nasal swabs from sequentially enrolled patients compared to a SARS CoV-2 extracted RT-PCR assay. Using NP swabs from banked specimens, the sensitivity was 80% (95% CI 68 to 88) compared to SARS-CoV-2 RT PCR assay.

WHO does not currently recommend the use of antigen-detecting rapid diagnostic tests for patient care, although research into their performance and potential diagnostic utility is highly encouraged (https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19).

Rapid antigen tests can potentially be used as an alternative to RT-PCR assay for the diagnosis of COVID-19 among symptomatic patients during the first week of illness. Negative results from an antigen test should be confirmed with an RT-PCR test prior to making treatment decisions to prevent undue transmission. Results should always be correlated with clinical and epidemiologic parameters.

C. Detection of Antibodies to SARS-CoV-2

Point of care and laboratory-based antibody immunoassays, with varying sensitivities and specificities, depending on the method used for detection (e.g. ELISA, chemiluminescence, lateral flow immunoassays) are now available.

Systematic review of 11 low quality studies (n=2660 samples) on **lateral flow immunoassays among patients infected with SARS-CoV-2 showed a pooled sensitivity of 66% (95% CI 49.3% to 79.3%).** Pooled analysis of 9 studies on ELISA (n=766 samples) yielded a pooled sensitivity of 84.3% (95% CI 75.6% to 90.9%) while pooled analysis of 2 studies on CLIA showed a pooled sensitivity of 97.8% (95% CI 46.2% to 100%). Point estimates of pooled sensitivity were lower for commercial kits versus in-house assays, for all three methods, with the strongest difference seen for LFIAs, where the sensitivity of commercial kits was 65.0% (95% CI 49.0% to 78.2%) and that of non-commercial tests was 88.2% (95% CI 83.6% to 91.3%). For all three test methods, pooled specificity was high when measured in populations where COVID-19 was not suspected, regardless of whether the sampling had been done before or during the epidemic. For both LFIAs and CLIAs, pooled specificity was lower among individuals with suspected COVID-19 compared with other groups(11).

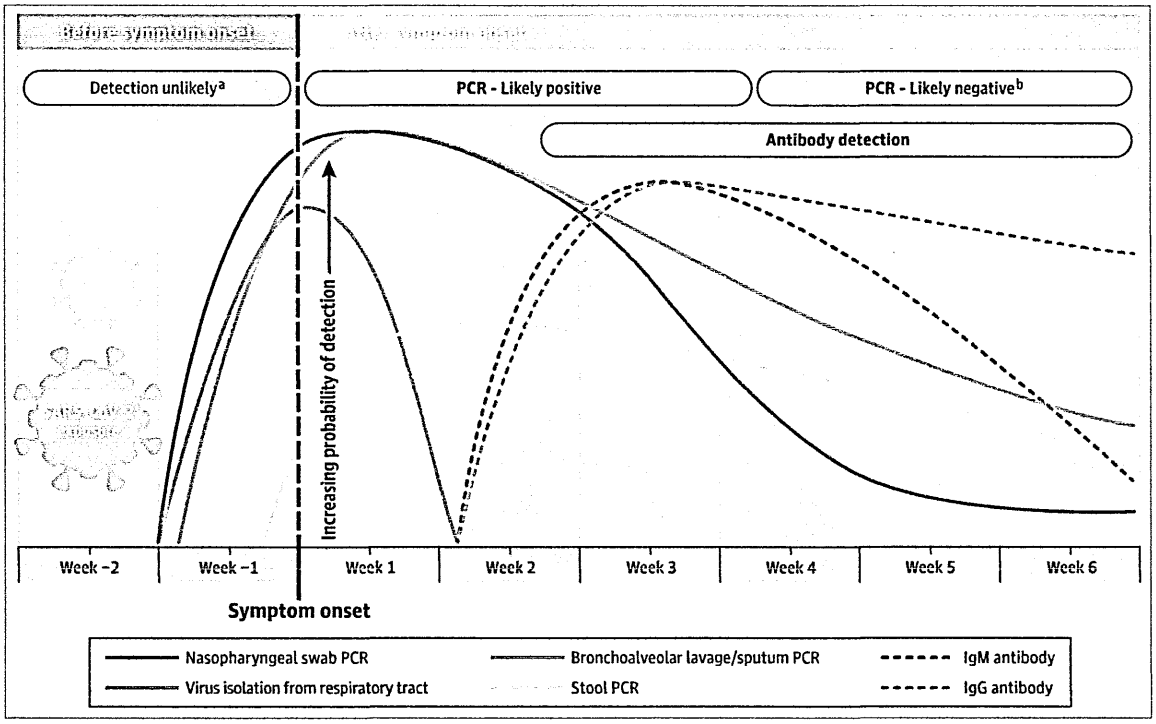
Pooled results for IgG, IgM, IgA, total antibodies and IgG/IgM all showed low sensitivity during the first week since onset of symptoms (all less than 30.1%), rising in the second week and reaching their highest values in the third week regardless of testing method. The combination of IgG/IgM had a sensitivity of 30.1% (95% CI 21.4 to 40.7) for 1 to 7 days, 72.2% (95% CI 63.5 to 79.5) for 8 to 14 days, 91.4% (95% CI 87.0 to 94.4) for 15 to 21 days and 96.0% (95% CI 90.6 to 98.3) for 22 to 35 days(12). However, it is still unknown whether antibodies persist following infection and whether the presence of antibodies confers protective immunity against future infection.

RECOMMENDATIONS:

- Rapid point-of-care lateral flow immunoassay antibody tests are not recommended as stand-alone tests for the diagnosis of COVID-19. These tests are also not recommended for mass testing and clearance for work of asymptomatic people due to its low sensitivity and high false negative rates.
- Laboratory based immunoassays such as chemiluminescence assay (CLIA) and enzyme-linked immunosorbent assay (ELISA) are the preferred tests for antibody determination. This is best done on the third week onwards from the onset of symptoms.

1. Only Food and Drug Administration approved and validated test kits with at least 90% sensitivity and 95% specificity should be used. The following website provides useful information regarding the laboratory performance of test kits - **https://www.finddx.org/covid-19/dx-data.**
2. Only medical doctors can prescribe and interpret the use of antibody-based and antigen-based test kits.

The timeline of diagnostic markers for the detection of COVID-19 infection in relation to symptom onset among immunocompetent adults is illustrated in Figure 1.



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Figure 1. Timeline of diagnostic markers for the detection of COVID-19 infection in relation to symptom onset

Source: Sethuraman N, Jeremiah S, Ryo A. Interpreting diagnostic tests for SARS CoV-2. JAMA May 6, 2020

Ancillary Tests

The following diagnostics are recommended when COVID-19 is suspected to guide management. Table 2 summarizes diagnostic tests, usual findings, and recommended frequency of monitoring:

- Complete Blood Count (CBC)
- Metabolic panel: creatinine, LFTs, sodium, potassium, magnesium, calcium, albumin
- Inflammatory markers: lactate dehydrogenase (LDH), Ferritin, C-reactive protein (CRP), and procalcitonin
- Prothrombin and D-Dimer
- Arterial blood gas (ABG) measurement
- Blood cultures if concomitant bacterial infection is suspected
- Respiratory tract specimen for influenza testing
- Sputum, endotracheal aspirate (ETA), or bronchoalveolar lavage fluid culture and sensitivity
- Chest x-ray
- High resolution chest CT scan plain
- ECG

Table 2: Summary of diagnostic tests for suspected, probable or confirmed Covid-19 disease

EPIDEMIOLOGIC RISK FACTORS	BASELINE DIAGNOSTICS	FINDINGS	FREQUENCY OF MONITORING	OTHER COMMENTS
LOW RISK (Mild disease)	***Mild symptoms, no pneumonia, no hypoxia***			
No comorbidities	None needed			Strict home isolation or quarantine in a designated COVID facility
MODERATE RISK	***With pneumonia but not oxygen requiring***			
HIGH RISK (Severe or critically ill)	***Pneumonia with SpO2<92, RR >30, SBP<90***			
Age >60 years *Pre-existing pulmonary disease* *CKD* *DM* *HTN or CVD* *Transplant*	***CBC***	Leukopenia or normal WBC Lymphopenia	Daily or as frequently as possible	If ALC <0.8, poor prognostic marker
	Complete metabolic panel	ALT/AST elevated Increased bilirubin Decreased albumin		
	Procalcitonin	Usually low or normal(13)		If elevated, consider other causes
	CRP	If low or normal consider other cause of ARF, or mild disease		* Can be used to track mortality risk (surviving patients

		If mean 66 mg/L, (IQR 48-98) higher risk of hypoxemia(5)	May repeat q 2-3 days to evaluate trend and/or when patient deteriorates	w/ median ~40 mg/L [IQR 10-60], non survivors w/ median 125 mg/L [IQR 60-160 mg/L] (5)
	D dimer			If >2.4 [IQR 0.6-14.4] increased risk of ICU stay(14)
	LDH	Elevated		If >245 IU- poor prognostic marker; If >400·0 (IQR 323·0–578·0), increased risk of ICU stay (14)
	PT/INR			
	Ferritin	Elevated		If >1000ng/ml, watch out for cytokine storm(15)
	Creatine kinase (CK)	May be elevated (13-33%) (14, 16)		
	Sputum or ETA GS/CS*	Usually normal flora	As clinically needed	Evaluate for bacterial cause
	Influenza A/B	Usually negative	No need to repeat	
	Respiratory viral panel*	Usually negative	No need to repeat	Can rule out other viral causes of pneumonia
	Blood and urine Cultures*	Usually negative	As clinically indicated	
	CXR PA/LAT	May be normal initially; bilateral Infiltrates most frequent and more common than a unilateral	May repeat in 3 days or if patient deteriorates	
	CT Chest	Ground glass opacities, typically bilateral (75%), but may be unilateral(14, 17) Other findings include peripheral distribution, fine reticular opacities and vascular thickening	Consider repeating periodically	Can detect early pneumonia before symptom onset (18) CT is more sensitive than radiography with 77 to 100% of patients with ground glass opacities [Bai HX 2020]. More sensitive than RT-PCR test [Ai T 2020, Fang Y 2020]

*If indicated or available

II. Collection of respiratory tract specimens

1. Personal Protective Equipment (PPE) for HCW collecting and handling respiratory tract specimens

   When collecting respiratory tract specimens, HCWs should wear the following PPE: eye protection, N95 or equivalent, double gloves, a disposable impermeable, breathable, long-sleeved, laboratory gown fastened at the back. If the specimen is collected through an aerosol-generating procedure, staff should wear a particulate respirator at least as protective as a NIOSH-certified N95, an EU standard FFP2, or the equivalent (19)

2. Procedure for collecting respiratory specimens(20)

   - Use sterile Dacron or rayon viral swabs for collecting upper respiratory tract specimens from both the nasopharynx and the oropharynx. Do not use calcium alginate swabs or cotton swabs with wooden shafts as these will inactivate the virus.

   - Collecting the OPS:

     1. Insert swab into the posterior pharynx and tonsillar areas. Rub swab over both tonsillar pillars and posterior oropharynx and avoid touching the tongue, teeth, and gums. Do not sample the tonsils.

   - Collecting the NPS:

     1. Patient must be seated upright, with the head in a straight position (not extended upwards/ not looking up because the pledget will be directed superiorly towards the anterior cranial base which can be dangerous)

     2. The pledget should be on a long orange stick.

     Gently insert flexible wire shaft swab through the nares parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the patient indicating contact with the nasopharynx. Gently, rub and roll the swab back. Leave the swab in place for several seconds to absorb secretions before removing. Do not sample the nostrils.

   - Lower respiratory tract specimens should be collected in sterile containers.

   - Avoid sputum induction to reduce the risk of aerosol transmission.

3. Specimen handling(20)

   - Place NP and OP swabs immediately into a sterile vial containing 2 mL of viral transport media without antibiotics. Both swabs can be placed in the same vial, if desired. Aseptically, cut or break applicator sticks off near the tip to permit tightening of the cap. Label the vial with the patient's name, specimen type, date collected and other required information.

- If specimens will be examined within 48 hours after collection, keep specimen at 4°C and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70°C and ship on dry ice.
- Avoid refreezing and thawing specimens.

4. Specimens should be packaged using the following triple packaging system (21):
   - Seal the primary receptacle containing the swabs and viral transport media using a semi-transparent flexible film (i.e. Parafilm). Wrap the primary receptacle with an absorbent material e.g., gauze.
   - Place the primary receptacle into the second container. The second container should be durable and leak-proof.
   - Place the second container into the outer container e.g., ice box. Ensure that the required temperature is maintained in the outer container through the use of wet ice or refrigerant packs.

5. All specimens for COVID-19 testing should be sent to the Research Institute for Tropical Medicine (RITM) by the health facility or to the designated sub-national laboratories and accredited private hospital laboratories. Sending of specimens for COVID-19 testing should be coordinated with the appropriate DOH-Regional Epidemiology and Surveillance Unit (RESU). The hotline mobile number for the RITM Surveillance and Response Unit is +63- 9478706673(20). Please refer to latest updates on which subnational laboratories and private hospital laboratories that have available RT-PCR tests for SARS-COV-2.

III. Equipment needed in units managing patients with suspected COVID-19 infection

- PPE
- Dedicated equipment including a thermometer, stethoscope and blood pressure apparatus
- Pulse oximeters
- Functioning oxygen systems
- Disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag)
- Video laryngoscopes/ laryngoscopes
- Closed suction system

NOTE: Use standard, contact, droplet/airborne precautions when handling contaminated oxygen interfaces of patients with COVID infection(19)

IV. Clinical presentation of patients with COVID-19 infection

1. Demographics of patients with COVID-19 infection

The following table (Table 3) describes the demographic characteristics of the first hundred hospitalized patients confirmed to have COVID-19 infection in Hubei, China. Since the spread of COVID-19 outside of Hubei, China, many other countries have verified local transmission and reported on the epidemiology of disease. In Korea, which had an abrupt increase in cases over a short period of time, the age distribution showed an M shape with two peaks in the age group of the 20s and 50s(22). Among the confirmed cases in Gyeonggi-do where the third-highest number of patients was observed, the peak age group was the 30's with a bell-shaped distribution. This is consistent with reports from China.

The median age of hospitalized patients varies between 47 and 73 years, with most cohorts having a male preponderance of approximately 60%.

Table 3. Summary of demographics of hospitalized patients with confirmed COVID-19

Demographics	Huang, et al (N=41)[14]	Chen, et al (N=99)[16]	Wang, et al (N=138)[17]
Age	49 years old (median)	55.5 years old (mean)	56 years old (median)
Gender (Male)	73%	68%	54.3%
Exposure to Huanan seafood market	66%	49%	8.7%
With underlying diseases	32%	51%	46.4%
Admitted to the ICU for respiratory support	32%	23%	26%

2. Incubation period and clinical symptoms of patients

A pooled analysis of 181 confirmed COVID-19 cases reported outside Hubei province, China between January to February 2020 showed that the median incubation period was estimated to be 5.1 days (95% CI, 4.5-5.8 days), with almost 98% of patients manifesting within 11.5 days (CI 8.2-15.6 days) of infection(23). The estimate of the dispersion parameter was 1.52 (CI, 1.32 to 1.72), with an estimated mean incubation period of 5.5 days(23).

Fever and cough were the most common symptoms first described among patients diagnosed with COVID-19 infection in Wuhan, Hubei Province, China. In the study by Wang et.al (17), 82% had dry cough. In the study by Chen, 90% of cases presented with more than one sign or symptom(16). In a more recent study of 151 cases, fever remained the most common symptom(6). Table 4 summarizes the common signs and symptoms of patients with COVID infection.

In a meta-analysis comprised of 10 studies from China (n= 50,466) (24) the incidence of

fever was 89.1%, cough occurred in 72.2%, and the incidence of muscle soreness or fatigue was 42.5%. Diarrhea, hemoptysis, headache, sore throat, shock, and other symptoms occurred only in a small number of patients.

Outside China, in the European Union, among 29 of their first cases, 20 reported fever, 14 reported cough and eight reported weakness(25). Additional symptoms included headaches (6 cases), sore throat (2), rhinorrhea (2), shortness of breath (2), myalgia (1), diarrhea (1) and nausea (1). Fever was reported as the sole symptom for nine cases. In 16 of 29 symptomatic cases, the symptoms at diagnosis were consistent with the case definition for acute respiratory infection, although it is possible that cases presented additional symptoms after diagnosis and these were not reported.

Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients. Anosmia or ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19(26). Anosmia or dysgeusia may precede the respiratory symptoms.

Table 4. Clinical signs and symptoms of patients with COVID-19 infection

Symptom/ Sign	Huang, et al(14) (N=41)	Chen, et al(16) (N=99)	Wang, et al(17) (N=138)	Zhou et al(6) (N=151)
Fever	98%	83%	98.6%	180 (94)
Cough	76%	82%	82% (dry cough)	151 (79)
Shortness of breath	55%	31%	31.2	NR
Muscle ache	44%	11%	34.8%	29 (15)
Confusion	NR	9%	NR	NR
Headache	8%	8%	6.5%	NR
Sore throat	NR	5%	17.4%	NR
Rhinorrhea	NR	4%	NR	NR
Chest pain	NR	2%	NR	NR
Diarrhea	3%	2%	10.1%	9 (5)
Nausea and vomiting	NR	1%	10.1% (nausea) 3.6% (vomiting)	7 (4)
Fatigue	NR	NR	69.6%	44 (23)

*NR – not reported

3. Clinical Course of Patients with COVID-19

The clinical course of patients with COVID-19 was followed from admission to discharge or death, in a recently published large retrospective cohort (6). Median time from illness onset to dyspnea was 13·0 days (9·0–16·5). Fever and cough were prolonged, with median duration of 12·0 days (IQR 8·0–13·0) and 19·0 days (IQR 12·0–23·0), respectively. Notably, 62 (45%) of survivors still had cough on discharge and 39 (72%) of non-survivors had cough at the time of death.

Sepsis developed at a median of 9·0 days (7·0–13·0) after illness onset among all patients, followed by ARDS (12·0 days [8·0–15·0]), acute cardiac injury (15·0 days [10·0–17·0]), acute kidney injury (15·0 days [13·0–19·5]), and secondary infection (17·0 days [13·0–19·0]). Figure 2 below (6) shows the course of survivors vs. non-survivors

In a large meta-analysis (24), the incidence of ARDS was 14.8% and severe cases in all infected cases occupied a percentage of 18.1%. The case fatality rate of patients with COVID-19 infection was 4.3%

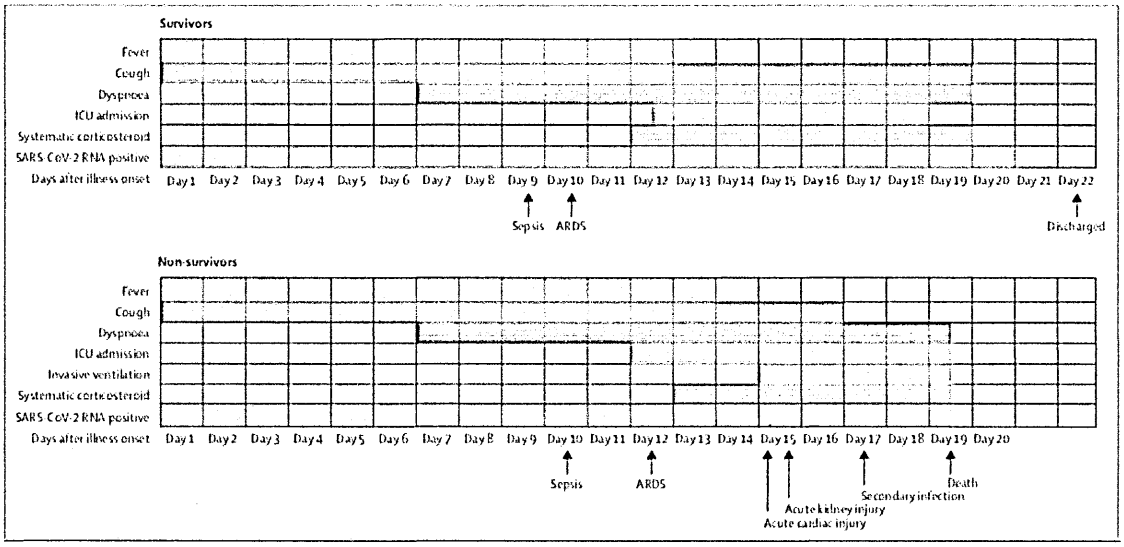


Figure 2: Clinical Course of COVID-19 Patients Among Survivors vs. Non-Survivors

4. Risk Factors for Poor Outcome

In a retrospective study of 191 patients(6), odds of in-hospital death were higher in patients with diabetes or coronary heart disease. Age, lymphopenia, leukocytosis, elevated ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin were also associated with death on univariate analysis. In a multivariable logistic regression model (n=171), older age, higher SOFA score, and D-dimer greater than 1 μg/mL at admission were associated with increased odds of death.

5. Course of Critically Ill Patients

In a smaller study(27) of 52 critically ill patients with confirmed COVID-19, the mean age of patients was 59·7 (SD 13·3) years, of whom most (35/52, 67%) were men, 21 (40%) of whom had chronic illness. Fever was the most common symptom (51/52, 98%). Overall mortality was high, at 61·5%, with patients' death occurring at 28 days; median duration from admission to the intensive care unit (ICU) to death was 7 (IQR 3–11) days for non-survivors.

Compared with survivors, non-survivors were more likely to be older (64·6 years [11·2] *vs* 51·9 years [12·9]), more likely to develop ARDS (26 [81%] patients *vs* 9 [45%] patients), and more likely to receive mechanical ventilation (30 [94%] patients *vs* 7 [35%] patients). Most patients had organ function damage, with ARDS being the most common [35 (67%)]. Notably, hospital-acquired infection occurred in seven (13·5%) of patients.

6. *Complications of Patients*

Data regarding the complications and outcome of individuals infected with COVID-19 remain limited to case series and reports. Majority of patients seem to recover. However, among the 99 cases described by Chen, et al(16), 17 (17%) patients developed ARDS of whom 11 (11%) patients worsened in a short period of time and died of multiple organ failure. Similarly, among the 41 cases reported by Huang et al (14), 13 (32%) patients were admitted to an ICU and six (15%) died. In the review of Wang, et. al(17), among 138 hospitalized patients, 36 (26.1%) were transferred to the ICU of which 22 (61%) developed ARDS. The mortality rate was 4.3%. Among cases reported globally, mortality is estimated at 2-3%. The elderly and individuals with underlying diseases have higher fatality rate compared to younger and healthier patients. A summary of complications and outcomes of these patients are in Table 5.

Table 5: Complications and Outcomes of Patients with Confirmed COVID-19

Outcome	Huang, et al(14) (N=41)	Chen, et al(16) (N=99)	Wang, et al (17) (N=138)
ARDS	12 (29) ^	17 (17)	27 (19.6)
Septic shock	3 (7)	4 (4)	12 (8.7)
Invasive ventilation	2 (5) *	4 (4)	17 (12.3)
ECMO	--	3 (3)	4 (2.9)
Discharged	28 (68)	31(31)	47 (34.1)
Death	6(15)	11 (11)	6 (4.3)

^ percent * combined ECMO/invasive ventilation
ARDS – acute respiratory distress syndrome; ECMO- Extracorporeal membrane oxygenation

V. Management of patients confirmed or suspected to have COVID-19

A. Surveillance Definitions: The following are the DOH case definitions for notification which transitions the reporting of PUI and PUM to Suspect, Probable, and Confirmed COVID-19 cases (Table 6). These definitions are consistent with the latest WHO Global Surveillance for COVID-19 disease interim guidance (as of March 20, 2020). The COVID-19 Surveillance System, through the DOH Epidemiology Bureau, will capture and detect cases through the enhanced influenza-like illness (ILI) and expanded severe acute respiratory infection (SARI) sentinel surveillance systems, notification from hospital and laboratory facilities, and event-based surveillance and response. Appropriate triage and referral of these cases should be made based on severity of illness (Figure 3).

a. **Suspect case** – is a person who is presenting with any of the conditions below:

   a. All SARI cases where NO other etiology fully explains the clinical presentation.
   b. ILI cases with any one of the following:
      i. With no other etiology that fully explains the clinical presentation AND a history of travel to or residence in an area that reported local transmission of COVID-19 disease during the 14 days prior to symptom onset
         OR
      ii. With contact to a confirmed or probable case of COVID-19 disease during the 14 days prior to the onset of symptoms

c. Individuals with fever or cough or shortness of breath or other respiratory signs or symptoms fulfilling any one of the following conditions:
    i. Aged 60 years and above
    ii. With a comorbidity
    iii. High-risk pregnancy
    iv. Healthcare worker

2. **Probable case** – a suspect case who fulfills anyone of the following listed below.
    a. Suspect case whom testing for COVID-19 is inconclusive
    b. Suspect who underwent testing for COVID-19 not conducted in a national or subnational reference laboratory or officially accredited laboratory for COVID-19 confirmatory testing
    c. Suspect case for whom testing could not be performed for any reason

3. **Confirmed case** – any individual, irrespective of the presence or absence of clinical signs and symptoms, who is laboratory-confirmed for COVID-19 in a test conducted at the national reference laboratory, a subnational reference laboratory, and/or officially accredited laboratory testing facility.

4. **Contact** - is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
    1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
    2. Direct physical contact with a probable or confirmed case;
    3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper PPE

Note: For confirmed asymptomatic cases, the period of contact is measured as the 2 days before, through the 14 days after the date on which the confirmatory sample was taken.

Table 6. Corresponding Old vs. New COVID-19 Case Definitions for Surveillance

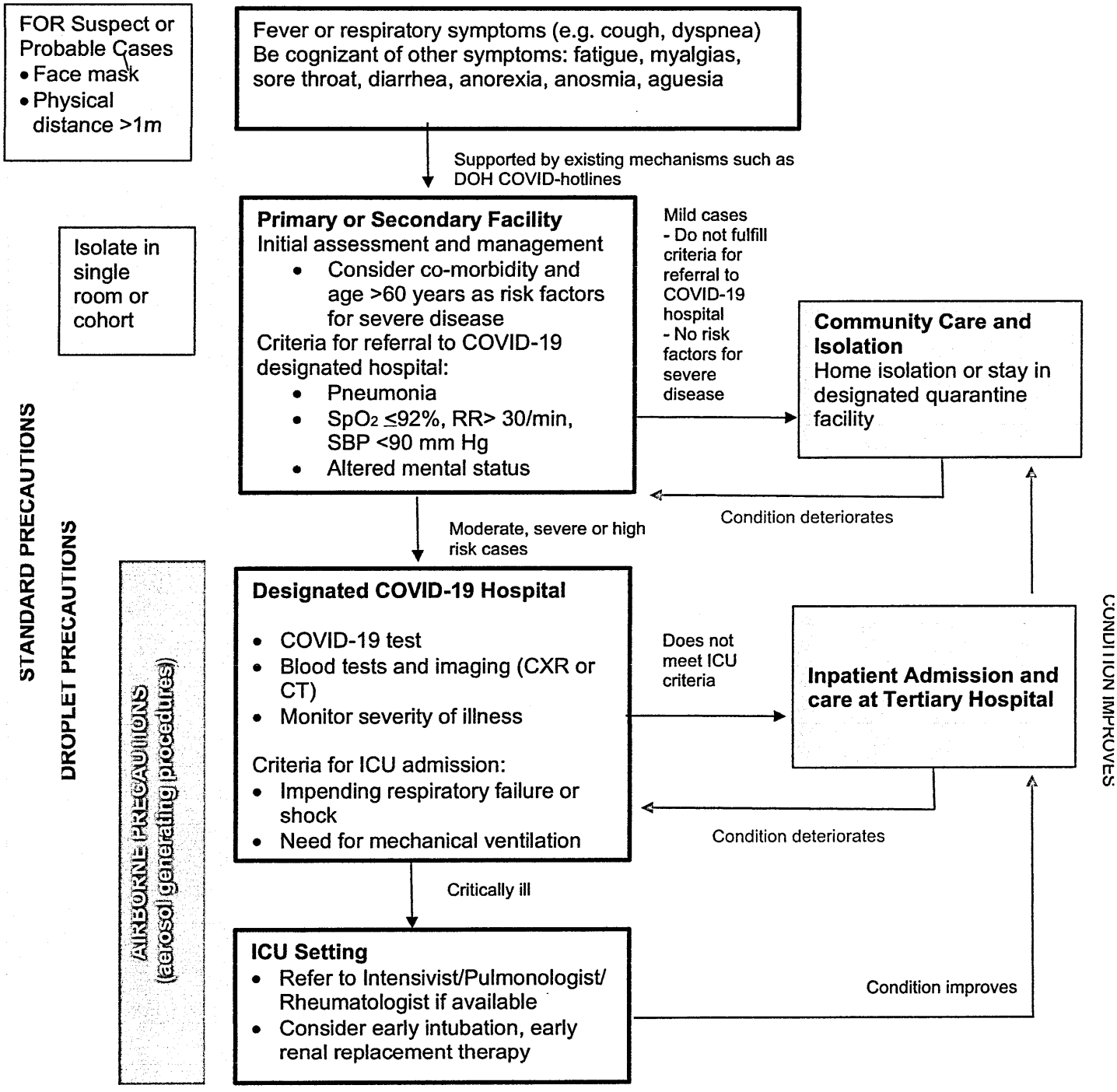
Old Classification	New Classification
Neither PUI nor PUM	Non-COVID case
PUM	Asymptomatic
PUI – mild, severe and critical who has not been tested and for testing	Suspect
PUI – mild, severe and critical with inconclusive, inadequate or no available testing	Probable
COVID-19 positive	Confirmed

Table 7. Disease severity classification of adult patients with probable or confirmed COVID-19 (Modified from WHO Interim Clinical Guidance May 2020)

Classification	Signs and Symptoms	Recommended Diagnostics	Management
Mild	Fever, cough, fatigue, anorexia, myalgias Other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms **NO signs of pneumonia or hypoxia**	SARS CoV-2 RT-PCR	Home isolation for 14 days with instructions or send to community quarantine facility. Admit if elderly or with unstable/uncontrolled co-morbid conditions. Give symptomatic treatment and supportive care as needed. Empiric antibiotics NOT needed
Moderate	With signs of Non-severe pneumonia (e.g. fever, cough, dyspnea or difficulty of breathing), RR 21-30/minute, SpO2 >92% on room air)	SARS CoV-2 RT-PCR CXR or CT scan CBC, ALT, AST, Creatinine ECG	Admit to a COVID-19 designated room/unit
Severe	Severe Pneumonia or severe acute respiratory infection, as follows: Fever, cough, dyspnea RR >30 breaths/minute, severe respiratory distress or $SpO_2 \leq 92\%$ on room air	SARS CoV-2 RT-PCR CBC Comprehensive metabolic panel Ferritin, LDH, Procalcitonin or CRP, INR/PT, D-dimer, Lactate CXR or CT scan Sputum GS/CS, Blood cultures, as appropriate ABG	See Section VI
Critical	Onset within 1 week of known clinical insult (pneumonia) or new or worsening respiratory symptoms, progressing infiltrates on CXR or chest CT, with respiratory failure not fully explained by cardiac failure or fluid overload (COVID-ARDS)	SARS CoV-2 RT-PCR CBC Comprehensive metabolic panel ABG Ferritin, LDH, Procalcitonin,	Consider COVID-19 ARDS – See Section VIII.

		CRP, INR/PT, D-dimer, Lactate Repeat CXR or CT scan ETA GS/CS, Blood cultures, as appropriate	
	Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, Signs of organ dysfunction: altered mental status difficult or fast breathing low oxygen saturation reduced urine output fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia		See Section VII
	Septic Shock: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level >2 mmol/L		

Figure 3. Algorithm for Covid-19 Referral and Triage ^



^Modified from WHO Algorithm for COVID-19 Referral and Triage

VI. Supportive Therapy and Monitoring for COVID-19 Patients with Pneumonia

- **Give supplemental oxygen therapy immediately to patients with severe pneumonia and /orrespiratory distress, hypoxemia, or shock and target SpO_2 >92%.**
  - Initiate oxygen therapy and titrate flow rates to reach target SpO_2 ≥92% during resuscitation.
  - Due to the possibility of increased viral transmission, the option to use HFNC (high-flow nasal cannula at 40-60 L/min) overlapped with surgical mask and non-invasive positive pressure ventilation (NIPPV) should be given to a patient in a single negative pressure room with the healthcare worker wearing complete PPE.
  - Suggest compute at 2, 6, 12H for ROX Index = ($SpO2/FiO_2$)/RR)
    - ≥4.88 - maintain O_2 support
    - <2.8 (2h), <3.47 (6H), <3.85 (12H) - perform intubation
  - Regularly assess the need for intubation and mechanical ventilation; if oxygenation does not improve using non-invasive methods, a trained and experienced provider (i.e. anesthesiologist) should perform endotracheal intubation under airborne precautions.
  - All areas where patients with pneumonia are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (simple face mask, and mask with reservoir bag).

- Keep the lung dry. Use conservative fluid management in patients with pneumonia when there is no evidence of shock.
  - Patients with pneumonia should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilators.

- Give appropriate empiric antimicrobials. Please refer to the Guidelines for the Diagnosis and Treatment of CAP in Adults (Annex C) for patients with community-acquired infection.
  - Although the patient may be suspected to have COVID-19, administer appropriate empiric antimicrobials within ONE hour of identification of sepsis.
- Streamline antimicrobial treatment as soon as microbiologic study results become available.

- Identify and properly manage other comorbidities

- Consider giving intravenous systemic corticosteroids (i.e., Dexamethasone 6mg/day for 10 days) for patients requiring O2 support based on results from the RECOVERY trial:
  - Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).

- Closely monitor patients with pneumonia for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately.

VII. Management of COVID-19 Acute Respiratory Distress Syndrome (CARDS)

A. Signs and symptoms

1. **Onset:** new or worsening respiratory symptoms within one week of known clinical insult
2. **Chest imaging (radiograph, CT scan, or lung ultrasound):** bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules
3. **Origin of edema:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of edema if no risk factor present

B. Classification of ARDS based on oxygenation among adults:

1. **Mild ARDS**: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH_2O, or non- ventilated)
2. **Moderate ARDS**: 100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O, or non- ventilate
3. **Severe ARDS**: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥5 cmH_2O, or non-ventilated).
4. When PaO_2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non-ventilated patients)

B. Management of COVID-19 ARDS

1. Admit the patient to the ICU.
2. Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy (28)
3. Severely hypoxemic patients should be monitored closely in an ICU setting for clinical deterioration and progression to ARDS and need for invasive mechanical ventilation. In these patients, intubation/ mechanical ventilation should be considered. For those with advance directives, non-rebreather masks may be an option.
4. Referral to the appropriate specialists (e.g. Pulmonologist and/or Intensivist) is highly recommended if COVID-19 ARDS is present.
5. Endotracheal intubation should be performed by a trained and experienced provider (i.e. an anesthesiologist), using airborne precautions and the appropriate PPE during intubation.
6. One-time intubation only using rapid sequence intubation (RSI) is ideal. Use of a video laryngoscope, when available, is optimal.
7. Bag-mask ventilation or mask ambubagging as pre-oxygenation is not recommended. Instead, place patient on 6L oxygen via nasal cannula.

8. Implement lung protection strategy with initial tidal volumes at 6-8 ml/kg of predicted body weight, provision of adequate PEEP for recruitment, while limiting inspiratory pressures (plateau pressures) below 30 cmH2O. Use of lower PEEP (<10 cmH_2O) is advised and caution exercised with higher PEEP (>10 cmH_2O).
9. COVID-19 ARDS patients who remain hypoxemic despite lung protection strategy should be immediately placed prone for no less than 12 hours with the goal of lung recruitment. Reassessment and the decision to terminate prone positioning after 12 hours should be made in consultation with a pulmonologist and/or an intensivist.
10. Keep lungs dry. Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.
    This is a strong guideline recommendation; the benefit is to shorten the duration of ventilation. (Philippine CPG on Sepsis 2020)
11. Intubated patients with moderate-severe ARDS (PaO_2/FiO_2 <150), neuromuscular blockade by continuous infusion should not be routinely used.
12. Extracorporeal life support (ECLS) should be considered when the above measures are unable to provide adequate oxygenation. Consider referral to a center with access to ECLS.
13. Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, de- recruitment and atelectasis. This may also facilitate aerosolization of viral particles.
14. Nebulization is not recommended; instead use metered dose inhalers, if necessary.
15. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).
16. Give anticoagulation therapy in the form of heparin or low molecular weight heparin for patients with D-dimer level of >1000.
17. A list of complications related to critical illness and how to prevent them is listed in Table 11.

VIII. Management of Severe Sepsis or Septic Shock

(Adapted from Philippine CPG on Sepsis 2020) (29)

- Admit the patient to the ICU.
- Give appropriate antimicrobials within one hour of initial patient assessment. Blood cultures should ideally be collected prior to antimicrobial treatment, but this should not delay administration of antimicrobials.
- Determine if infection was acquired in the community or in the hospital setting and provide appropriate empiric therapy, based on clinical presentation. (Annex C: Guidelines for the Diagnosis and Treatment of CAP in Adults for patients with community-acquired infection).
- Early effective fluid resuscitation as follows:
    - In adults, administer at least 30 mL/kg of isotonic crystalloid in adults in the first 3 hours.
    - Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.
    - Monitor for volume overload during resuscitation. Fluid overload can lead to respiratory failure.

- Apply vasopressors when shock persists in the form of: Norepinephrine (1st) or vasopressin (2nd), and possibly dobutamine (3rd) if signs of poor perfusion and cardiac dysfunction persist
- The initial blood pressure target is MAP ≥65 mmHg in adults. Use of vasopressors should not be delayed especially after adequate fluid resuscitation.
- If central venous catheters are not available, vasopressors can be given through a peripheral IV access, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion.
- Consider using intravenous corticosteroids for refractory shock.
- Discuss end of life issues with the family in case of deterioration of clinical condition.

IX. Investigational Therapies for The Treatment of COVID Pneumonia

The evidence on the use of specific therapy against SARS-CoV2 is currently limited. The **core management recommendations remain to be supportive care and intensive respiratory management.** Below is a summary discussion of the anti-viral drugs, immunomodulating agents and adjunct therapies currently under investigation. Further evidence review of these therapies can be found in https://www.psmid.org/rapid-evidence-review-on-covid-19-management/.

Should any of these investigational therapies be considered, a thorough review of the benefits and safety considerations should be discussed by the attending physician with the patient and his/her family and/or the patient's legally authorized representative. Further, a signed informed consent should be obtained before use. All outcomes related to the use of investigational drugs outside of a clinical trial setting should be reported to the Philippine FDA.

For patients with mild COVID-19 disease, symptomatic treatment is recommended. These include antipyretics for fever, oral fluids for hydration, isolation at home or in temporary treatment and monitoring facilities. Routine empiric antibiotics and anti-influenza drugs are NOT recommended.

Drugs with anti-SARS CoV-2 activity

A. Remdesivir (RD):

1. *Mechanism of Action* - RD, formerly GS-5734, is a monophosphate prodrug that undergoes metabolism in cells and tissues to an active C-adenosine nucleoside triphosphate analogue that binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has been recently recognized as a promising antiviral drug due to its broad-spectrum, potent in-vitro activity against several coronaviruses, including SARS-CoV-2, SARS and MERS-CoV. (30, 31)

2. *Evidence Summary*

The first clinical use of remdesivir was for the treatment of Ebola(32); followed by a case report (33) and case series (34) describing the outcome of treatment with remdesivir among hospitalized patients with moderate to severe COVID-19. The case series involved 53 patients with confirmed SARS-CoV-2 infection and with oxygen saturation ≤ 94%, who received a 10-day course of RD through compassionate use (34). Thirty-six patients (68%)

had an improvement in oxygen-support, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated and 7 (13%) died (34).

Literature search conducted up to May 28, 2020 yielded three published randomized clinical trials (RCTs) (35-37) and four ongoing RCTs(38, 39) . **Pooled analysis of two RCTs (35, 36) involving 1,296 patients with severe/hospitalized COVID-19 which evaluated outcomes at day 28, showed that remdesivir had a faster time to clinical improvement by 3 days (Mean Difference: -2.80, 95%CI: -4.92, -0.68) with a corresponding increase in the recovery rate (Rate Ratio 1.30, 95%CI: 1.12, 1.51) compared to placebo. However, no significant effect on mortality based on the hazard ratio (HR 0.78, 95%CI: 0.56, 1.07) was seen** (38). The results of this pooled analysis is driven mainly by the recently published preliminary report from the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT-1), a multicenter adaptive, double blind randomized controlled trial of 1,063 patients (RD =541 and placebo =522) from the United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore (35). The ACTT trial showed that the median time to recovery was shorter with remdesivir than with placebo (11 days versus 15 days), with a statistically significant rate ratio of 1.32 (95% CI, 1.12 to 1.55). The Kaplan- Meier estimates of mortality after 14 days, however, was not significant at 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death = 0.70; 95% CI, 0.47 to 1.04). At the time of analysis, 301 participants (28%) have yet to complete the study while 208 (20%) were still on treatment. Likewise, no information on the use of cointerventions (supportive pharmacotherapies and treatments directed at COVID-19) throughout the trial was reported. It is unclear what standard of care was given in addition to RD. This preliminary report was the basis of the US and European FDA emergency use authorization among patients with severe COVID-19.

The second RCT of 237 severe COVID-19 patients in Wuhan, China showed no significant difference in time to clinical improvement (HR 1.25; 95% CI: 0.88 to 1.78) and mortality (RR 1.08; 95%CI 0.54 to 2.18). This phase III randomized, double-blind, placebo-controlled trial was terminated because of lack of patients to be enrolled into the study with the control of the outbreak in Wuhan(36).

In both RCTs, remdesivir was given intravenously as a 200 mg loading dose on day 1, followed by 100 mg dose once daily for the next 9 days. Patients who had elevated ALT (alanine transferase) or AST (aspartate aminotransferase) > 5x upper normal limit, severe renal impairment based on GFR or on dialysis, and pregnant/breastfeeding women were excluded.

The third RCT (GS-US-540-5773) is a preliminary report of an ongoing trial which showed that the time to clinical improvement and recovery did not differ significantly between the five-day treatment and 10-day treatment regimen(37). This trial did not have a placebo control group.

3. RECOMMENDATIONS:

- Remdesivir may be considered in the setting of a clinical trial for hospitalized adult patients with severe COVID-19 or for compassionate use, pending publication of the full report from the ACTT trial and the result of the ongoing WHO Solidarity trial.

- The dosing regimen for remdesivir is 200 mg IV loading dose (infused over 30 minutes) on Day 1 followed by 100 mg IV (infused over 30 minutes) for 5-10 days.
- For hospitalized patients with severe COVID-19 who are not intubated, a five-day regimen of remdesivir may be given.
- There is insufficient data to recommend routine use of remdesivir among patients with mild to moderate COVID-19 disease except in the context of a clinical trial.

B. Chloroquine or hydroxychloroquine (CQ or HCQ):

1. ***Mechanism of action*** - CQ is a 4-aminochloroquine used mainly as an anti-malarial agent, while HCQ is used for autoimmune diseases such as SLE and rheumatoid arthritis. HCQ differs from CQ only by hydroxylation at the end of the side chain and they have the same mechanism of action. A systematic review of 6 in-vitro studies provided pre-clinical evidence on the efficacy of CQ as an inhibitor of SARS-CoV2 (40). CQ and HCQ appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Both drugs have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells(40, 41). However, the clinical safety profile of hydroxychloroquine is better than that of chloroquine during long-term use, allows higher daily dose and has fewer side effects and is a more potent inhibitor of SARS CoV 2 in-vitro based on physiologically-based pharmacokinetic models(42).

2. ***Evidence Summary-***

Systematic review of three small RCTs (43-45) and three quasi-experimental studies (46-48) showed that hydroxychloroquine and chloroquine were not associated with a difference in overall mortality when compared to standard care for COVID-19 but may result in a shorter time to intubation, death, and ventricular arrythmia.

HCQ compared to standard of care

- Meta-analysis of 2 small RCTs (43, 44) with high risk of bias showed small improvement in chest CT findings (RR 1.41, 95% CI 1.03, 1.92), but there was no significant difference in clinical outcomes such as disease progression (49)among patients with moderate to severe COVID pneumonia. There were no reported deaths at 7 days (45) and at 14-28 days (44, 45)
- One small quasi-experimental study (47) reported little or no difference in all-cause mortality at 7 days between the group of patients with moderate/severe COVID-19 treated with HCQ and those receiving standard care (RR 0.93, 95% CI 0.48 to 1.81). The same study also reported little or no difference in time to death between both groups (HR 1.20, 95% CI 0.42 to 3.45, N=173)
- Another large quasi-experimental study done in one center in New York, USA showed no difference in time to mechanical intubation or death (HR 0.98, 95% CI 0.73, 1.31)(46). Another small quasi-randomized study of 63 patients concluded that HCQ was associated with an increased need for escalation of respiratory support among hospitalized patients with COVID-19 and that there were no benefits of hydroxychloroquine on mortality, lymphopenia, or neutrophil-to- lymphocyte ratio improvement(48).
- Metaanalysis of 2 small RCTS also showed an increased risk of adverse events during days 14-28 (RR 2.49, 95% CI 1.04 to 5.98, 2 RCTs, N=180, low certainty evidence) (44, 45)

A large multinational registry analysis (50) recently published in Lancet showed that hydroxychloroquine/chloroquine with or without macrolide and hydroxychloroquine with

macrolide compared to standard of care may result in increased risk of in-hospital mortality, shorter time to intubation/mechanical ventilation or death and shorter time to ventricular arrhythmia. However, this observational study has been retracted by the authors because of issues on the veracity of the primary data sources(50)

There are no published studies on HCQ plus lopinavir/ritonavir to date but there are six ongoing trials on HCQ plus lopinavir/ritonavir [rapid review]. There are 39 ongoing trials on HCQ plus azithromycin, 73 trials on HCQ, 15 trials on CQ for the treatment of COVID-19, 37 ongoing trials on HCQ combined with other drugs. [CADTH 2020]

Preliminary results of the RECOVERY trial released on June 5, 2020 concluded that hydroxychloroquine does not reduce the risk of death among hospitalized patients with COVID-19. A total of 1,542 patients were randomized to hydroxychloroquine and compared with 3132 patients randomized to usual care alone. **There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes**. The RECOVERY trial is a large randomized controlled trial conducted in the UK.

Preliminary analysis of data from the WHO Solidarity trial also showed no significant difference on in-hospital mortality among 912 patients randomized to HCQ (144 deaths,15.6%) compared to 882 patients randomized to local standard of care (108 deaths,12.2%) with a hazards ratio of 1.30 (99% CI 0.93-1.80).

3. *RECOMMENDATION* – Chloroquine (CQ) or hydroxychloroquine (HCQ) as monotherapy or in combination with a macrolide (e.g. azithromycin) or an antiviral agent (lopinavir-ritonavir, favipiravir) is NOT recommended for hospitalized patients with probable or confirmed COVID-19 pneumonia.

C. Lopinavir-ritonavir:

1. *Mechanism of Action* - Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor administered in fixed-dose combination with ritonavir (LPV/r), a potent CYP3A4 inhibitor that increases lopinavir concentration. Chu *et al.* (51) found that LPV/r has anti-SARS-CoV activity *in vitro* and in clinical studies via inhibition of 3-chymotrypsin-like protease, thus preventing viral replication. Although LPV/r has in vitro activity against SARS-CoV, it has poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition in vivo. Lopinavir is excreted in the GIT, and thus coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.

2. *Evidence Summary*

Literature search yielded 2 small open-label RCTs on lopinavir/ritonavir for COVID-19.

- In a study comparing 111 patients with severe acute respiratory syndrome (SARS) treated with ribavirin monotherapy and 41 patients with SARS treated with LPV/r and ribavirin combined therapy, patients under the combined therapy had a lower risk of acute respiratory distress syndrome (ARDS) and death. Currently, LPV/r had been tried in some case series (3, 51, 52), and at least 17 clinical trials are also underway, including a WHO-initiated multinational trial.
- The LOTUS China (Lopinavir Trial for Suppression of SARS-Cov-2 in China) RCT included 199 adult patients hospitalized with severe Covid-19. In the intention-to-treat (ITT) population, LPV/r treatment within 12 days after the onset of symptoms was associated with shorter time to clinical improvement (HR=0.78, 95% CI 0.63

to 0.97) but beyond 12 days no difference in clinical improvement was seen in either the ITT analysis (HR 1.31, CI 95% 0.95-1.85) or MITT (HR 1.39, CI 95%, 1-1.91) compared to standard of care. Mortality did not also differ significantly between the 2 groups (HR=0.67, 9%% CI 0.38 to 1.17) but respiratory failure or ARDS was significantly higher in the standard of care group compared to the LPV/r group.

- The ELACOI trial (53) was a small 3-arm controlled pre-print trial which evaluated the efficacy and safety of LPV/r against arbidol and standard of treatment alone among mild/moderate COVID-19 patients. No significant difference was seen with regards to time to negative conversion of COVID-19 nucleic acid, rate of defervescence, cough improvement and radiologic improvement at day 7 and day 14 among the three arms.
- Most common adverse events were nausea, vomiting, diarrhea, increased cholesterol and triglyceride levels

Preliminary results of the RECOVERY trial released on June 29, 2020 concluded that lopinavir/ritonavir has no beneficial effect among hospitalized patients with COVID-19 disease. A total of 1,596 patients were randomized to lopinavir-ritonavir and compared with 3376 patients randomized to usual care alone. Of these patients, 4% required invasive mechanical ventilation when they entered the trial, 70% required oxygen alone, and 26% did not require any respiratory intervention. There was no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58) and the results were consistent in different subgroups of patients. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay.

Preliminary analysis of the SOLIDARITY trial also showed no significant difference on in-hospital mortality rate among 1343 patients randomized to lopinavir/ritonavir (177 deaths, 13.2%) compared to 1293 patients randomized to local standard of care (143 deaths, 11.1%) with an odds ratio of 1.21 (95% CI 0.91 to 1.62).

3. ***RECOMMENDATION:*** Lopinavir/ritonavir as monotherapy or in combination with hydroxychloroquine or immunomodulators or an antiviral agent is NOT recommended for hospitalized patients with probable or confirmed COVID-19 pneumonia.

D. Favipiravir

1. *Mechanism of Action* – Favipiravir, (6-fluoro-3-hydroxy-2pyrazinecarboxamide, Avigan) is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5'-triphosphate. The active agent selectively inhibits the RNA-dependent RNA polymerase, halting viral replication. As a prodrug, favipiravir, was shown to effectively inhibit the SARS-COV-2 infection in clinical isolates in vitro.

2. *Evidence Summary*

- There are no published placebo-controlled trials on favipiravir.
- One small open-label pre-print RCT showed no significant difference in clinical recovery rates of favipiravir (n=116) versus umifenovir (n=120) among patients with moderate to severe COVID-19. (54)
- One small pre-print open-label non-randomized trial showed that administration of favipiravir (n=35) compared to lopinavir/ritonavir (n=45) resulted in earlier viral

clearance (4 vs 11 days) and more patients with chest CT scan improvement (91% vs 62%) among non-severe COVID-19 patients. Both groups received interferon-alpha 1 beta by aerosol inhalation(55).

- Both these pre-print studies, however, have high risk of bias.
- There are at least 9 ongoing clinical trials on favipiravir either as monotherapy or in combination with immunomodulators.

3. ***RECOMMENDATION***: There is insufficient evidence to recommend routine use of favipiravir for the treatment of COVID-19 except in the context of a clinical trial or for compassionate use. The clinical trial dosing regimen is 1,800 mg 2x/day loading dose then 800 mg 2x/day for 13 days.

Immunomodulating Agents

A. Corticosteroids

1. *Mechanism of action* – Corticosteroids inhibit multiple inflammatory cytokines resulting in decreased edema, capillary leakage, and migration of inflammatory cells, thereby globally suppressing the inflammatory response.

2. Evidence –preliminary results comparing dexamethasone **6 mg given once daily for up to ten days** vs. usual care alone from The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial, a randomized, controlled, open-label, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19 have been released (56):
   - In the trial, 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age- adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001).
   - The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14).
   - The study concluded that in patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support.

3. RECOMMENDATIONS –

- There is moderate quality evidence to recommend the use of corticosteroids particularly dexamethasone as adjunctive treatment for patients with COVID-19 requiring oxygen support. The recommended regimen is dexamethasone 6 mg IV for ten days.
- Inhaled steroids are NOT recommended for the treatment of COVID-19 pending the results of ongoing studies.

- Oral, inhaled or IV steroids are NOT recommended for prophylaxis or prevention of COVID-19.

B. Interferon

1. *Mechanism of action* – Interferons (IFNs) refer to innate cytokines that make host cells refractory to virus replication. There have been clinical studies on the efficacy of type I interferons, alfa and beta, in the treatment of SARS-CoV with variable results. Studies on the effects of these treatments on survival of patients with MERS-CoV have not shown significant benefits.

2. *Evidence* –
   - One small pre-print randomized open label clinical trial involving 103 severe COVID-19 patients in Iran showed no difference in time to clinical improvement between the interferon group and standard of care group. However, early administration significantly reduced mortality (OR=13.5; 95% CI: 1.5-118) while, late administration of INF did not show significant effect (OR=2.1; 95% CI: 0.48-9.6). More patients were extubated in the IFN group (p=0.019) and the 28-day overall mortality was significantly lower in the IFN then the control group (19% vs. 43.6% respectively, p= 0.015). Standard of care included HCQ, lopinavir/ritonavir, steroids and IVIG(57).
   - There are 2 retrospective cohort studies(58, 59), one involving children and the other adults, both with mild to moderate COVID-19, where IFN-b was given by aerosolization. In the cohort with children (58), improvement of pneumonia was noted 4-10 days after initiation, with or without lopinavir/ritonavir. In the adult cohort, there was reduction in the duration of detectable SARS CoV-2 in the upper respiratory tract(59).
   - An open-label, randomized, phase 2 trial examined the effect of interferon beta-1b with and without lopinavir/ritonavir and ribavirin among 127 patients with mild to moderate COVID-19. The primary endpoint was time to negative naso-pharyngeal swab for SARS-CoV-2 RT-PCR. Results showed that triple therapy of IFN beta-1b, lopinavir/ritonavir and ribavirin was associated with a significant reduction in the duration of viral shedding (time to negative nasopharyngeal swab 7 days [IQR 5–11] in the combination group *vs* 12 days [8–15] in the control group; hazard ratio [HR] 4·37 [95% CI 1·86–10·24]), symptom alleviation (0 of 4 days [IQR 3–8] *vs* 8 days [7–9]; HR 3·92 [1·66–9·23]), and duration of hospital stay (9·0 days [7·0–13·0] *vs* 14·5 days [9·3–16·0]; HR 2·72 [1·2–6·13]) (60)

3. *Recommendation*: There is insufficient evidence to support the routine use of IFNs for hospitalized patients with COVID-19 except in the context of a clinical trial or for compassionate use.

C. Tocilizumab and other Il-6 inhibitors

1. *Mechanism of Action* – Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that specifically binds sIL-6R and mIL-6R and inhibits signal transduction. It is currently used mainly for rheumatoid arthritis (61). The results of long-term toxicity tests on animals showed that tocilizumab was well tolerated, and no significant abnormalities were observed in other clinicopathological studies or histopathological evaluations (61-63).

Other similar IL-6 inhibitors include leronlimab, sarilumab and siltuximab. Siltuximab is a chimeric monoclonal antibody approved for treatment of adults with multicentric Castleman's disease who are negative for HIV and human herpes virus-8. Sarilumab is a human IgG1 monoclonal antibody that has been approved by the FDA for rheumatoid arthritis.

2. Evidence Summary

- In a multicenter retrospective cohort of 544 patients in Italy with severe COVID-19 pneumonia, tocilizumab administered either intravenously or subcutaneously was associated with reduced risk of mechanical ventilation or death (adjusted HR 0.61. 95% CI 0.40 to 0.92) compared to standard of care. a significant reduction in risk of death was found for tocilizumab treatment compared with standard of care treatment alone after controlling for sex, age, SOFA score, recruiting center, and duration of symptoms (adjusted HR 0·38, 95% CI 0·17–0·83)(64)
- In a small observational retrospective study (65), a single infusion of Tocilizumab given to severely or critically ill COVID-19 patients (n=21) resulted in prompt improvement in clinical, inflammatory and radiologic markers.
    - Patients had normalization of body temperature (21/21), improvement in lymphocyte counts (10/19) and CRP levels (17/18), and improvement in CT imaging findings and lung function (19/21)
- There is no completed RCT yet on tocilizumab use for COVID-19; 7 trials are ongoing.
- A single-center case-control study on the use of siltuximab in adult COVID-19 patients with ARDS is ongoing (NCT04322188).
- At present, there are no data from clinical trials on the efficacy of sarilumab for patients with COVID-19.

*3. **RECOMMENDATION:*** There is insufficient evidence to recommend the routine use of tocilizumab or other IL-6 inhibitors for severe COVID-19 patients suspected to be in cytokine storm except in the context of a clinical trial or for compassionate use.

E. Convalescent Plasma (CP)

1. *Mechanism of action* – This refers to the administration of antibodies against SARS-CoV-2 with the use of plasma from recovered COVID-19 patients. It is a means of antibody transfer to provide passive immunity (through neutralizing antibodies or possibly other immune mediators directed against the infectious pathogen) until the individual can develop an active immune response, with the hope that clinical outcomes can be improved in the recipient.
This mode of passive antibody therapy had been previously used to provide immediate immunity to susceptible individuals against pandemic viruses such as SARS, MERS, A(H1N1) influenza and Ebola. The efficacy of this therapy has been associated with the concentration of neutralizing antibodies (Nabs) in plasma from recovered donors. In SARS-CoV and MERS, NAbs bind to spike1-receptor binding protein (S1-RBD), S1-N-terminal domain and S2, thus inhibiting their entry, limiting viral amplification

2. *Evidence* –

In the Philippines, convalescent plasma is approved for compassionate use among severe COVID-19 patients. A clinical trial has also been approved which will investigate the efficacy and safety of convalescent plasma in preventing disease progression and ICU admission among hospitalized COVID-19 patients. Specific criteria must be met to be

eligible for CP donation (Annex B)

- A recently completed open-label RCT conducted in Wuhan, China among 103 patients with severe or life-threatening COVID-19 showed that convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement (52 versus 43 percent, HR for improvement 1.4, 95% CI 0.79-2.49) and mortality (16 versus 24 percent, odds ratio [OR] 0.65, 95% CI 0.29-1.46) within 28 days. However, the trial may have been underpowered to detect a clinically important difference because of early termination of the trial due to poor enrollment. Although convalescent plasma improved the rate of nasopharyngeal viral RNA clearance at 72 hours compared with standard treatment alone (87 versus 38 percent), there were no statistically significant differences in the overall rates of clinical improvement or mortality by 28 days. Among the subset of patients who had severe but not life-threatening disease, the rate of clinical improvement was greater with convalescent plasma (91 versus 68 percent, HR 2.15, 95% CI 1.07-4.32)(66).
- A Cochrane rapid review of 1 RCT and 3 non-randomized studies on the effectiveness of convalescent plasma showed no significant differences in all-cause mortality, time to death and improvement of clinical symptoms(67).

3. ***RECOMMENDATION***: There is insufficient evidence to support the routine use of convalescent plasma for critically ill COVID-19 patients except in the context of a clinical trial or for compassionate use.

F. Intravenous Immunoglobulin G

1. Mechanism of Action – Intravenous immunoglobulin G (IVIg) is a mixture of polyclonal immunoglobulin and proteins pooled from healthy donors. Its mechanism of action is twofold – one, as a neutralizing antibody and second as an anti-inflammatory or immunomodulator of the cytokine response (e.g. IL-1 or TNF-α).

2. Evidence – There are no randomized controlled trials on the use of IVIg among COVID-19 patients.

- Three patients (68) were successfully treated with high-dose IVIg at the early stage of clinical deterioration. The authors suggest that a high dose of IVIg at 0.3-0.5 g/kg BW daily for 5 days administered at the appropriate point could successfully block the progression of the disease cascade and improve the outcome of COVID-19.
- In another case series (69) ten COVID-19 patients receiving short-term moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d) were studied.
    - Short-term moderate-dose corticosteroid (160mg/d) plus immunoglobulin (20g/d) was found to be effective for reversing the continued deterioration of COVID-19 patients who failed to respond to the low-dose therapy, based on statistically significant improvement in the APACHE II score, body temperature, lymphocyte count, lactate dehydrogenase, and CRP levels.

3. ***RECOMMENDATION:*** There is insufficient evidence to support the use of IVIg for the treatment of COVID-19 except in the context of a clinical trial.

G. Hemoperfusion

1. *Mechanism of action* – Cytokine release syndrome is prevalent in severe cases of COVID-19. Hemoperfusion devices or extracorporeal blood purification has been proven to effectively remove the released inflammatory cytokines.

2. Evidence –
   - There are currently no published trials on the effectiveness and safety of hemoperfusion as an adjunctive treatment for severe COVID-19.
   - There is a published case report on the successful use of continuous renal replacement therapy with hemoperfusion in a 54 year-old male in Iran, with documented clinical improvement and decrease in inflammatory markers after 3 sessions of CRRT with hemoperfusion(70) .

3. ***RECOMMENDATION:*** There is insufficient evidence to recommend the routine use of hemoperfusion as adjunctive treatment for COVID-19.

Adjunctive Therapy

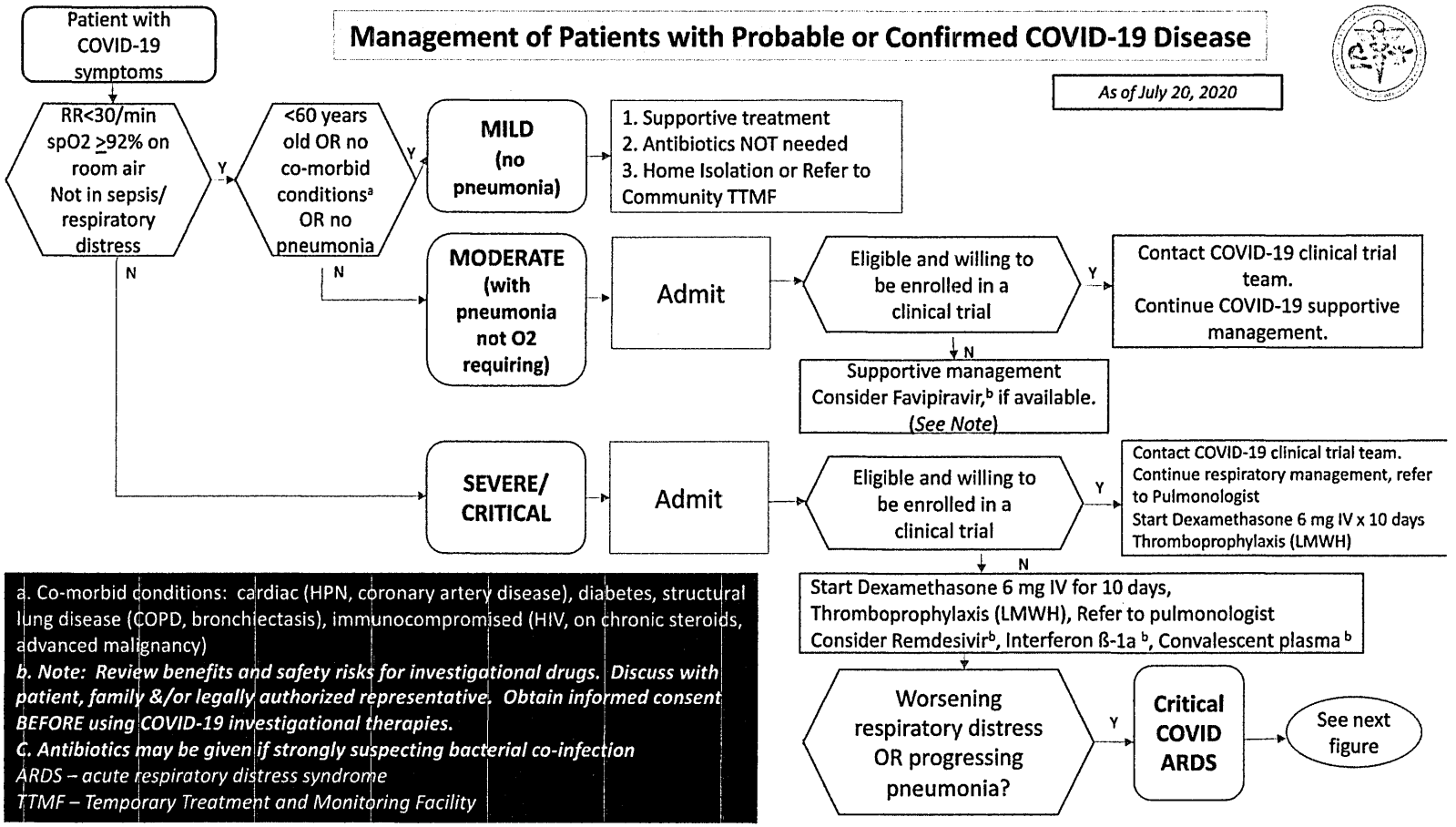
Vitamin C and zinc

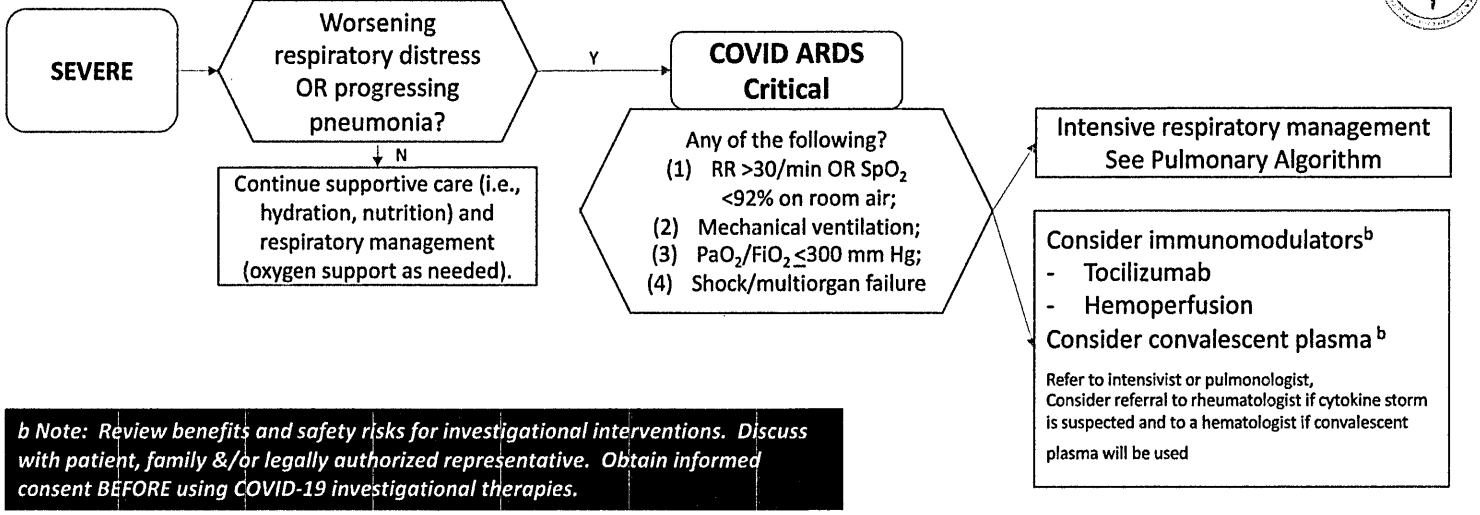
1. *Mechanism of action* – Vitamin C is a water-soluble vitamin with antioxidant properties. In in –animal studies, it is thought to attenuate organ induced injury. Zinc is an essential mineral used to boost the immune system.

2. Evidence –
   - There is no direct evidence available at this time on the efficacy/effectiveness of intravenous vitamin C in reducing mortality or shortening disease course among adults suspected of, or positive for COVID-19.
   - Indirect evidence based on studies in non-COVID-19 conditions (e.g. common colds) may not be applicable due to differences in pathophysiology and interaction with other factors like comorbidities may further modify the effect of the intervention. Indirect evidence from studies in sepsis and ARDS do not show any benefit.
   - There are no clinical studies that have assessed the use of Zinc or zinc compounds as direct or adjunctive treatment of COVID-19 infection.

3. ***RECOMMENDATION*** - There is insufficient evidence to recommend the use of Vitamin C and zinc as adjunctive treatment for COVID-19.

Figure 4: Management Algorithm





Management of Patients with Probable or Confirmed Severe COVID-19 Pneumonia

ALGORITHM IN THE RESPIRATORY MANAGEMENT OF CRITICALLY ILL WITH SUSPECTED &/OR CONFIRMED COVID-19

PCCP Council on Critical Care and Pulmonary Vascular Disorders *As of July 19, 2020*

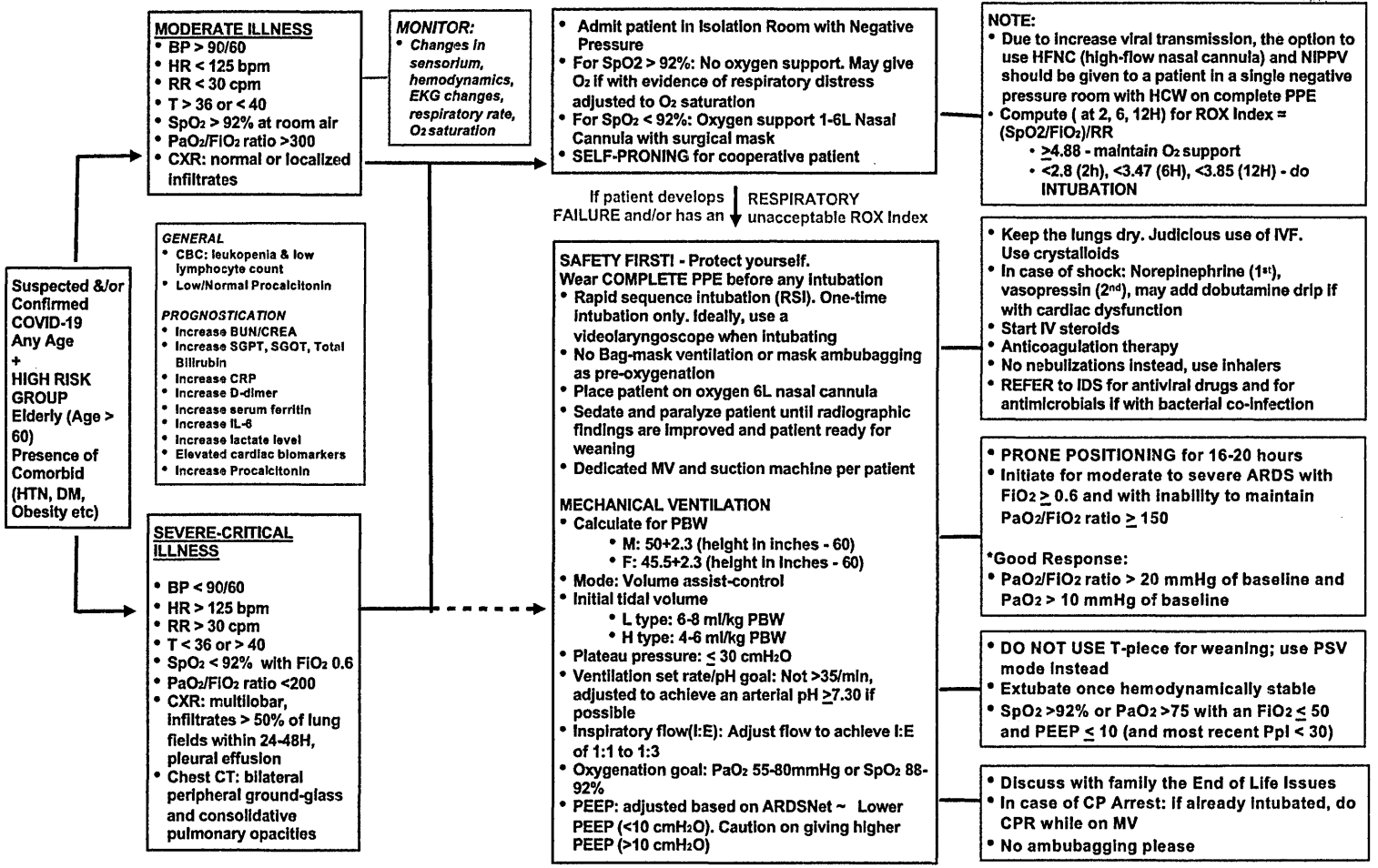


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Table 9: Guidance on the Use of Tocilizumab*

INDICATIONS		CONTRAINDICATIONS	MONITORING
May use a combination of clinical and diagnostic criteria		**ABSOLUTE**	**BEFORE STARTING***
Clinical Criteria(71)	***Diagnostic Criteria (15)^***		
Severe	T> 38.4°C Hepato- or splenomegaly Any bicytopenia Triglycerides >1.5 mmol/l Fibrinogen <2.5g/L Ferritin >1000 ng/ml	ALT >5x ULN ANC < 0.5 10^9/L Platelet <50 10^3/uL Hypersensitivity to the drug	Screen for TB, Hepatitis B and C (HBsAg, anti-HBc IgM/IgG, anti HCV)
RR >30 SpO2≤ 92 PaO2/FiO2 <300			
Critical			**PERIODICALLY**
Respiratory failure requiring mechanical ventilation Shock Organ failure ICU admission			CBC Ferritin CRP LDH ALT/AST

LEGEND: ALT – alanine aminotransferase; ANC – absolute neutrophil count; ULN – upper limit of normal
^ May use H score calculator (predictive of cytokine storm): http://saintantoine.aphp.fr/score/
* Should not delay treatment. Refer to Rheumatologist if suspecting cytokine storm

X. Adverse Drug Reactions (ADR) and Monitoring while Using Investigational Therapy For COVID-19

A. Adverse Drug Reactions(72-75)

1. **Remdesivir** – elevated creatinine, elevated AST/ALT

2. **Tocilizumab** – This can cause hypertension (4-6%), diarrhea, abdominal pain (2-3%), increase in ALT/AST (0.7-48%), dizziness (2-3%), headache (5-7%), pharyngitis (4-7%) or infusion reactions (7-22%). Serious side effects include thrombocytopenia (1-4%), neutropenia (1.8-3.7%), GI perforation, pancreatitis, hepatotoxicity, and anaphylaxis. It can also lead to upper respiratory infections (5-8%) or severe infectious diseases.

3. **Favipiravir** - mild diarrhea and nausea, elevated serum uric acid, elevated AST/ALT and elevated bilirubin

B. Monitoring

1. **Remdesivir** – Monitor liver enzymes and creatinine.

2. Tocilizumab

2.1 Evaluate for latent/active TB prior to initiation.
2.2 Check baseline CBC, and ALT/AST and monitor periodically.
2.3 Check baseline lipid panel and monitor periodically
2.4 Do Hepatitis B, anti-HCV and TB screening at the minimum.

XI. Dosing Regimen and Duration of Investigational Drugs

Table 10: Dosing Regimen and Duration of Investigational Drugs

REMDESIVIR	FAVIPIRAVIR*	TOCILIZUMAB*	Dexamethasone	Interferon ß-1a
200 mg IV loading dose (infused over 30 min) on Day 1 followed by 100 mg once daily IV (infused over 30 min) maintenance dose Recommended remdesivir dosing duration is a total of 5 -10 days.	1800 mg 2x/day loading dose then 800 mg 2x/day for 13 days	4-8mg/kg single dose with recommended dose of 400mg IV diluted in 0.9 NSS to 100mL, given as a 2-hour infusion A single extra dose may be given after 12 hours at the discretion of the provider (76).	6 mg once daily for 10 days	Interferon ß-1a administered intravenously at the dose of 10 µg once daily for 6 days. OR Interferon ß1a administered subcutaneously at the dose of 44 µg on Day 1, Day 3 and Day 6 (total: 3 doses). It should be given at the same time each day. No dosage adjustment is required for renal or hepatic impairment.

**The optimal doses required for treatment of COVID-19 is not yet established.*

XII. Pre-exposure or Post-exposure prophylaxis for COVID-19

Chloroquine or hydroxychloroquine is NOT recommended for pre-exposure or post-exposure prophylaxis to prevent COVID-19. There is no high-quality direct evidence at this time to support the use of chloroquine or hydroxychloroquine for prophylaxis. Published data are in-vitro and derived from experience on malaria. There are at least four ongoing clinical trials on the effectiveness of HCQ as a prophylaxis for COVID-19.

One randomized, double-blind, placebo-controlled trial on the use of HCQ as post-exposure prophylaxis, which was conducted in the United States and Canada among 821 asymptomatic adults with unprotected household or occupational exposure to a person with confirmed COVID-19 at a distance of less than 6 ft for more than 10 minutes showed no significant difference in laboratory-confirmed or probable COVID-19 infection among participants exposed to COVID-19 who received HCQ prophylaxis compared to placebo (RR 0.83, 95% CI: 0.58 to 1.18). HCQ was given as 800 mg once, then 600 mg 6 to 8 hours later, then 600 mg daily for 4 more days. HCQ significantly increased the risk for adverse events compared to placebo (RR 2.39, 95% CI: 2.83 to 3.11). Common adverse events reported were gastrointestinal (nausea, abdominal discomfort or vomiting, diarrhea), neurologic (irritability, dizziness or vertigo), and headache(77).

Priority protective measures to protect health care workers include proper wearing of PPE, providing rational working shifts for each team (every 4-8 hour-shifts) and providing rest periods for the health care team. **Supply of good quality PPEs should be ensured for our health care workers. Measures to ensure that our health care workers' mental and physical health are taken cared of should be in place. These include: rotation of health teams to allow**

adequate rest periods, psychosocial support, buddy system to ensure that PPEs are properly worn, proper management of HCW exposures and access to testing.

XIII. Prevention of Complications

Implement the following interventions to minimize complications associated with critical illness (Table 11).

Table 11: Interventions for Prevention of Complications(28)

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize 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	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30-45°) • 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 mobilize the patient early in the course of illness when safe to do so

XIV. Recommendations for repeat testing for COVID-19

1. Repeat testing after a positive COVID-19 test

There is no gold standard "test of cure" for COVID-19. Based on available guidelines (78), a test-based or symptom-based strategy may be used. For the test-based strategy, two consecutive RT-PCRs more than 24 hours apart will be used to document recovery and virologic clearance or virologic shedding.

Currently, the need for documenting 2 consecutive PCRs is being questioned in light of recent evidence showing that although viral shedding can last several weeks (79), the virus is likely non-viable by day 8 as demonstrated in viral cultures (80). The US-CDC acknowledges that detecting viral RNA via PCR does not necessarily mean that infectious virus is present (78). Recently, the Korean CDC also performed over 100 consecutive cultures from patients who were found to be PCR positive again after repeat testing, after recovery and release from isolation. All cases were negative for viral culture and there was no single confirmed case among contacts of all positive cases (Korean CDC).

Since RT-PCR positivity persists significantly beyond infectivity, routine repeat testing or a test-based approach may lead to unnecessary isolation and use of PPE and testing resources. The odds of a positive culture were decreased by 32% for each unit increase in cycle threshold value. At Ct values ≥ 34 infectious viral particles were not detected(82). Another study showed that no positive viral cultures were seen at a Cycle Threshold Value of **≥ 24.** No positive viral cultures were documented in symptom to test days of greater than 8 DAYS (83). Hence, the proposed cutoff to assess non-infectivity is a Ct value of > 30.

Repeat testing after a positive COVID-19 test is no longer recommended at this time. A time or symptom-based strategy for discharge (Section XV) and return to work (Section XVI) are preferred.

2. **Repeat testing after an initial negative COVID-19 test in a symptomatic patient**

Repeat testing for patients with an initial negative COVID-19 test result should be performed ONLY if there is a high index of suspicion for COVID-19 infection, despite an initial negative test result. Such conditions include, but are not limited, to the following:

a. Clinical deterioration in the presence of an established disease etiology and with adequate treatment. A single negative test result, particularly if this is from an upper respiratory tract specimen, does not exclude infection. Repeat sampling and testing, preferably of lower respiratory specimen, is strongly recommended in severe or progressive disease. Consider a possible co-infection with COVID-19.

b. No other etiology for the patient's signs and symptoms has been identified despite work-up.

c. Clinical specimen(s) initially sent was/were deemed to be unsatisfactory or insufficient (delay in transport and processing, only NPS or OPS was sent).

XV. Criteria for Discontinuation of Transmission based Precautions and Discharge

A. **Criteria for discontinuation of transmission-based precautions (including isolation)**

1. Transmission-based precautions and isolation of hospitalized patients under an institutional COVID-19 care pathway may be discontinued **10-14 days after symptom onset, plus at least 3 days without symptoms (no fever and respiratory symptoms).**

2. Release from a COVID-19 care pathway is NOT the same as clinical discharge from a facility or from one ward to another.

   This recommendation is adapted from the WHO Interim Guidance on the Clinical Management of COVID-19 (May 27, 2020).

3. *Test-based strategy for specific patient groups*

   A test-based strategy could be done, preferably in consultation with local infectious diseases experts, because of concerns about the patient being infectious longer than usual. This group of patients include:

   - Persons who could pose a risk of transmitting infection to vulnerable individuals at high risk for morbidity or mortality from SARS-CoV-2 infection, or who support critical infrastructure (for continuing critical operations).
   - Persons normally residing in congregate living facilities (e.g., correctional/detention facilities, retirement communities, ships) where there might be increased risk of rapid spread and morbidity or mortality if spread were to occur.
   - Persons who are immunocompromised as we do not know yet the transmission dynamics and if prolonged viral shedding equates to infectivity in this population. These conditions include patients on chemotherapy for cancer, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days.
   - Other less immunocompromising conditions such as end-stage renal disease, diabetes mellitus, advanced age may be considered depending on the patient's circumstances and assessment of the health care provider

   For these patients, transmission-based precautions and isolation may be discontinued if:

   i. 10-14 days after symptom onset, plus at least 3 days without symptoms (no fever and respiratory symptoms).

   ii. A negative RT PCR test done on day 14 from the date of onset of symptoms. If still positive, repeat RT PCR at least 24 hours apart until there is documentation of at least one negative RT PCR. Consultation with an ID specialist may be considered for persistently positive PCR results.

B. Symptom-based Criteria for Facility Discharge of Immunocompetent Patients with Probable or Confirmed COVID-19

1. A repeat negative RT-PCR test is no longer needed for discharge of immunocompetent patients with suspect, probable or confirmed COVID-19 regardless of severity.

2. Patients who have clinically recovered (with resolution of symptoms) may be discharged from the hospital at the discretion of the healthcare team, once all of the following conditions are met:

    a. No fever or use of antipyretic medications for at least 3 days (>72 hours)
    b. Clinical improvement for at least 3 days (e.g. no longer oxygen-requiring, improvement of respiratory symptoms)
    c. At least 10-14 days have passed since the first symptoms appeared for patients with mild-moderate illness
    d. For severe and critical patients, at least 21 days have passed since the first symptoms appeared

3. Consultation with an infectious disease specialist is recommended if there are concerns that patients may be infectious beyond 21 days.

C. Health management of discharged patients

1. For discharged patients, close follow-up is still required.
2. When a patient is discharged from the hospital, his place of residence and address should be recorded and the local government unit informed.
3. Patient instructions:
    - Continue to wear mask, practice cough etiquette, and maintain physical distancing at home.
    - If fever and / or respiratory symptoms recur, the corresponding primary health care facility should assist in sending them to the designated medical institutions in the area for assessment and treatment. This should be reported to the corresponding surveillance units of the Department of Health.

XVI. Health management of asymptomatic individuals with confirmed COVID-19

A. Immunocompetent individuals

- These asymptomatic individuals should remain under home (or community facility) quarantine for 10 days from the time they tested positive for COVID-19. **There is no need for a COVID-19 test (i.e. PCR, or serology) at end of quarantine.**

B. Immunocompromised individuals, special groups (see list in Section XV.A.3), and those who tested positive as part of any screening strategy (i.e. before surgery) or contact tracing

- Repeat RT PCR as early as 10 days from the initial positive RT PCR. A single negative RT PCR can be used to discontinue transmission-based precautions (including isolation). If still positive, repeat RT PCR at least 24 hours apart until there is documentation of at least one negative RT PCR.

NOTE: Should asymptomatic individuals develop fever or respiratory symptoms within this 10-day quarantine period, quarantine should be extended for 10 days after the first day of symptoms. Follow test-based strategy for specific groups prior to discontinuation of transmission-based precautions.

XVII. Recommendations for Confirmed COVID-19 Healthcare Workers Returning to Work

Either a *test-based strategy* or a symptom based strategy for healthcare workers (HCW) returning to work may be used (Adapted from CDC)(81).

1. SYMPTOMATIC HCW

A. Test-based strategy - Because of the increased risk of transmission in the healthcare setting, a test-based strategy for HCW is preferred:

- Resolution of fever without the use of fever-reducing medications **and**
- Improvement in respiratory symptoms (e.g., cough, shortness of breath), **and**
- Negative results of COVID-19 molecular assay for detection of SARS-CoV-2 RNA from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens)

B. Symptom based strategy – All HCW with COVID-19 should be excluded from work until all the following conditions are met:

- at least 3 days (72 hours) have passed *since recovery* defined as resolution of fever without the use of fever-reducing medications **and**
- continuous improvement in respiratory symptoms for at least 3 days (e.g., no cough, no shortness of breath, non-oxygen requiring, radiographic improvement); **and**,at least 10-14 days have passed *since symptoms first appeared.*

2. ASYMPTOMATIC HCW

A. Time-based strategy - Exclude from work until:

- 10-14 days have passed since the date of their first positive COVID-19 diagnostic test assuming they have not subsequently developed symptoms since their positive test.
- If they develop symptoms, then the *symptom-based* or *test-based strategy* should be used.

B. Test-based strategy - Exclude from work until:

- Negative results of COVID-19 molecular assay for SARS-CoV-2 RNA RT PCR from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens). Because of the absence of symptoms, it is not possible to gauge where these individuals are in the course of their illness. There have been reports of prolonged detection of RNA without direct correlation to viral culture.

Since RT-PCR positivity persists significantly beyond infectivity, routine repeat testing or a test-based approach may lead to unnecessary isolation and use of PPE and testing resources. The odds of a positive culture were decreased by 32% for each unit increase in cycle threshold value. At Ct values ≥ 34 infectious viral particles were not detected(82). No positive viral cultures were seen at a Cycle Threshold Value of **≥ 24.** No positive viral cultures were documented in symptom to test days of greater than 8 DAYS (83).

The qualitative reporting of results of SARS-CoV-2 RT-PCR as positive or negative is sufficient for diagnosis but may be supplemented by reporting the cycle threshold (Ct), a semi-quantitative value, as well as time of symptom onset to guide duration of isolation or quarantine and clearance for work, return to school, clearance for medical or surgical procedures.

XVII. Guidelines on Advance Directives (Do Not Resuscitate or Allow Natural Death Orders) for Patients with Severe COVID-19 infection

1. The medical team may withhold cardiopulmonary resuscitation for critically ill patients with NO reasonable chance of recovery: these include COVID-19 Acute Respiratory Distress Syndrome secondary to High-Risk Pneumonia and not responding to treatment, refractory septic shock, or multi-organ failure.

2. The free and informed decision not to resuscitate made by a competent patient through an advanced directive should be followed.

3. Without the patient's advanced directive, the free and informed decision of an appropriate proxy of an incompetent patient should be followed.

4. Without a patient's or a proxy's decision, the medical team can make the decision based on futility, the best interest of the patient, and scarcity of resources.

5. Efforts must be made to provide spiritual care and counseling for the patient and family.

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Annex A
Informed Consent Template (if no clinical trial is available)

INFORMED CONSENT FOR OFF-LABEL USE OF MEDICATION/S AND/OR USE OF INVESTIGATIONAL DRUG/S FOR COVID-19

Dr. _____ *[Name of physician]* is offering to treat you, your child (in which case the word "you" will refer to "your child" throughout this document), or the person you represent (in which case the word "you" will refer to the person you are representing) with _____ ***[Name of unapproved drug, device, or biologic]*** because you have been clinically diagnosed with probable or confirmed SARS-CoV2 infection, called COVID-19, and there are no standard acceptable drugs at present.

What you should know about this treatment using COVID-19 investigational drug
This treatment has not been approved by the Food and Drug Administration.
For drugs approved for medical use by the Philippine Food and Drug Administration (FDA), the manufacturers' packaging labels, or inserts, state the condition or conditions for which they may be used. Physicians may opt for off-label drug use when convinced that it is for the patient's best interests, and the patient is well-informed and expresses his/her consent for its use, its composition, contraindications, and side effects.
This treatment is considered experimental.
This treatment is not research and you will not be considered a research subject.
Someone will explain this treatment to you.
You give consent to get this treatment.
Whether or not you get this treatment is up to you.
You can choose not to get this treatment.
You can agree to get this treatment now and later change your mind.
If you do change your mind, contact your doctor right away.
Whatever you decide it will not be held against you.
Feel free to ask all the questions you want before you decide.

How long will this treatment last?
We expect that the experimental treatment will last _____ *[days/until a certain event]*.

What happens if I get this treatment?
[Tell the patient what to expect using lay language and simple terms.]

Is there any way this treatment could be bad for me?
[Describe the risks of the treatment]
This treatment may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.
If you are or become pregnant, this treatment may hurt your baby or your pregnancy in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

Can this treatment help me?
We cannot promise that this treatment will cure you. The goal of this treatment is to _____. ***[Describe the potential benefits of the treatment]***

What else do I need to know?
Efforts will be made to limit your personal information, including medical records, to people who have a need to review this information. Organizations that may inspect and copy your information include appropriate representatives of the _____***[Name of hospital]***, and the FDA or appropriate government agency.
If you are injured or made sick from taking part in this treatment, medical care will be provided. Generally, this care will be billed to you or your insurance. However, it is possible that your insurance will not pay for the care, because the treatment is experimental or with use of investigational drug. Contact your doctor for more information.

Who can I talk to?
If you have questions, concerns, or complaints, or think the treatment has hurt you, you can talk to your doctor at _____ ***[Insert contact information]***

This treatment is subject to oversight by this hospital's Institutional Ethics/ Review Board/ Committee. If you have questions about your rights or any unresolved question, concerns, or complaints, talk to them at _____ ***[Insert contact information]***.

Your signature documents your permission to take part in this experimental treatment.

Signature of person providing consent (patient, legally authorized representative, parent, or guardian)	Date
Printed name of patient	
Printed name of person providing consent, if patient is unable to consent	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Annex B
Donor Criteria for Convalescent Plasms

In line with the Department of Health Memorandum 2020-0126 on the "Collection of Convalescent Plasma (CP) and Networking for Therapeutic Strategy for COVID-19", the voluntary donor for COVID-19 convalescent plasma must fulfill the following criteria to be eligible for CP donation:

1. Passed the standard DOH-prescribed donor history questionnaires, where applicable, with weight of at least 50 kg and age range of 18 to 65 years old

2. Recovered from COVID-19 with the following order of preference for donors

1st priority	• Previously diagnosed with COVID-19 by SARS-CoV-2 RT-PCR • Absence of any clinical evidence of COVID-19 for at least 14 days as determined by a licensed physician • With at least 1 negative SARS-CoV-2 RT-PCR result done on recovery
2nd priority	• Previously diagnosed with COVID-19 by SARS-CoV-2 RT-PCR • Absence of any clinical evidence of COVID-19 for at least 28 days as determined by a licensed physician • Even without a negative SARS-CoV-2 RT-PCR result done on recovery
3rd priority	• No SARS-CoV-2 RT-PCR test done to document disease • Absence of any clinical evidence of COVID-19 for at least 28 days as determined by a licensed physician • Positive result for anti-SARS-CoV-2 IgG antibody-based test done on recovery

3. Negative for anti-HLA antibodies, for donors with prior transfusions and female donors with prior history of pregnancy

4. Meet additional laboratory parameters:
    a. Hemoglobin greater than or equal to 12.5 g/dL for females or 13.5 g/dL for males
    b. Platelet count more than or equal to 150,000/mm3
    c. When available, donors should be positive for SARS-CoV-2 IgG with a titer of at least 1:160. (A titer of 1:80 may be considered acceptable if an alternative matched unit is not available)

5. Must have signed the informed consent for donation