Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

March 31 2020

DEPARTMENT MEMORANDUM
No. 2020 - 0138

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; DIRECTOR GENERAL OF PHILIPPINES INSTITUTE OF TRADITIONAL MEDICINE AND ALTERNATIVE HEALTH CARE; CHIEFS OF MEDICAL CENTERS, HOSPITALS, SANITARIA AND INSTITUTES; PRESIDENT OF THE PHILIPPINE HEALTH INSURANCE CORPORATION; DIRECTORS OF PHILIPPINE NATIONAL AIDS COUNCIL SECRETARIAT AND TREATMENT AND REHABILITATION CENTERS AND ALL OTHERS CONCERNED**

SUBJECT: **Adoption of PSMID Clinical Practice Guidelines on COVID-19**

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan City, China in December 2019 as a cluster of pneumonia cases of unknown etiology. With the increasing number of cases and deaths in various territories, the World Health Organization declared COVID-19 as a pandemic last March 11, 2020.

As of March 29, 2020, the Philippines has recorded 1,500 confirmed cases of COVID-19 with 77 deaths and 42 recoveries. This highlights the need to enhance protocols on the clinical management of COVID-19 cases to improve patient outcomes. Hence, the DOH hereby adopts the Clinical Practice Guidelines (CPG) on COVID-19 by the Philippine Society for Microbiology and Infectious Diseases (PSMID). (See ***Annex A***)

PSMID's CPG on COVID-19 shall be used in the clinical management of COVID-19 cases in all hospitals and health facilities, both public and private, subject to continuous update by the society.

Dissemination of the above information is requested.

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

ANNEX "A"

Philippine Society for Microbiology and Infectious Diseases

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

Version 2.1, as of 31 March 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 March 28, 2020, there were more than >571,000 cases worldwide, with 26,494 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. Out of 202 confirmed cases, 19% were imported from outside of the Philippines, 14% were categorized as localized transmission, and the remaining cases are unknown or still under investigation. Of these 17 deaths have been reported (2). Since then, there has been a surge of cases to over 1,000 confirmed cases as of March 28, 2020 with sustained local transmission in the National Capital Region. Of the 1,419 confirmed cases reported on March 29, there were 71 deaths reported.

The clinical presentation of SARS CoV-2 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 (3-6). Treatment is largely supportive, although in-vitro and early retrospective data regarding the off-label use of several compounds, such as remdesivir (RD/GS-5734), chloroquine (CQ), hydroxychloroquine (HCQ), lopinavir-ritonavir (LPV/r) and tocilizumab (TCZ) show promise.

This document is written with the intention to guide clinicians managing COVID-19 cases. It is based on early 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.

I. Diagnostic testing

All individuals with suspected SARS COV-2 respiratory tract infection i.e., Patients Under Investigation (PUIs), should undergo testing for COVID-19 as well as other tests warranted by their clinical condition.

Tests for COVID-19

A. Real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay – the currently recommended test to confirm COVID-19 infection is an rRT-PCR assay, which can be used to detect the virus. 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.

B. COVID-19 IgG and IgM Rapid Diagnostic Test (RDT) kits - the Food and Drug Administration (FDA) approved the use of antibody-based test kits for SARS-CoV2 testing on March 30, 2020. Based on the single study by Li et. al., [8] the RDT kit has a sensitivity of 88.86%, and specificity of 90.63%. The seemingly high positive predictive value of the test is due to the high prevalence of COVID-19 in this study which is greater than 75%. The true accuracy of immunoassays for COVID-19 has not been established yet. The likelihood of false negative results from immunoassays in general should be considered. Furthermore, analytical specificity and sensitivity have not yet been determined as stated by the authors. Cross reactivity with other coronaviruses and flu viruses as well as the detection limit have not yet been determined. Based on this single, low quality evidence, there is insufficient evidence to use the kits as stand-alone kits for definitive diagnosis of COVID-19 and it cannot be used for mass testing.

Hence, the kit can only be used only under the following conditions:

1. Only Food and Drug Administration (FDA) approved kits should be used.
2. A COVID-19 antibody test CANNOT be used as a stand-alone test to definitively diagnose COVID-19 and CANNOT be used for mass testing.
3. The COVID-19 RDT can only be used in people who had onset of symptoms for at least 5 days (i.e. for IgM) and 21 days (i.e. for IgG). Most kits include both IgM and IgG, so they can be used by day 5.
4. Anyone who tests positive for IgM should be tested with an RT-PCR to confirm the positive test.
5. A negative IgM test DOES NOT rule out COVID-19 and the symptomatic patient should REMAIN ISOLATED and swabbed using RT-PCR for confirmation.
6. IgG-only positive individuals without RT-PCR should be labeled as presumptive past COVID-19 and not be officially counted as confirmed unless there is a further validation test in the future, or if validated with a PRNT (Plaque reduction neutralization test) or viral culture by a third party.

   If a patient is symptomatic, an RT-PCR should be done, and the patient should be quarantined.

   If a patient is asymptomatic, there is no need to test using an RT-PCR.
7. The IgG antibody can be used as an adjunct test to clear quarantined patients who

remain asymptomatic at 14 days post discharge. The presence of antibodies typically indicates viral clearance. If IgG is positive, the patient can be released from self-quarantine. If IgG is negative, a repeat RT-PCR should be performed

8. ONLY medical doctors can prescribe and interpret the use of the antibody-based test kits. These kits will not be available over the counter.

Other Tests:

The following diagnostics are recommended when COVID-19 is suspected to guide management. Table 1 summarizes diagnostic tests, usual findings, and recommended frequency of monitoring:

- Complete Blood Count (CBC)
- Blood tests for creatinine, LFTs, sodium, potassium, magnesium, calcium, albumin and inflammatory markers such as 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 1: SUMMARY OF DIAGNOSTIC TESTS FOR SUSPECTED, PROBABLE OR CONFIRMED COVID-19 CASES[9]

EPIDEMIOLOGIC RISK FACTORS	BASELINE DIAGNOSTICS	FINDING	FREQUENCY OF MONITORING	OTHER COMMENTS
LOW RISK (Mild disease)	***Mild symptoms***			
No comorbidities	None needed			Strict home isolation or quarantine in a designated COVID facility
HIGH RISK (Severe or critically ill)	***Fever with or without respiratory symptoms 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	Daily or as frequently as possible	If ALC <0.8, poor prognostic marker
	Complete metabolic panel	ALT/AST elevated		
	Procalcitonin	Usually low or normal(10)		If elevated, consider other causes

	CRP	If low or normal consider other cause of ARF, or mild disease If mean 66 mg/L, (IQR 48-98) higher risk of hypoxemia(5)	May repeat q2-3 days to evaluate trend and/or when patient deteriorates	* Can be used to track mortality risk (surviving patients 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 (11)
	LDH			If >245 IU- poor prognostic marker; If >400·0 (IQR 323·0–578·0), increased risk of ICU stay (11)
	PT/INR			
	Ferritin			If >1000ng/ml, watch out for cytokine storm(12)
	Creatine kinase (CK)	May be elevated (13-33%) (11, 13)		
	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	May repeat in 3 days or if patient deteriorates	
	CT Chest	Ground glass opacities, typically bilateral (75%), but may be unilateral (11, 14)	Consider repeating periodically	Can detect early pneumonia before symptom onset (15)

*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.(16)

2. Procedure for collecting respiratory specimens(17)

   - 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:

     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(17)

   - 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 4ºC and ship on wet ice or refrigerant gel-packs, otherwise store frozen at ≤-70ºC and ship on dry ice.
- Avoid refreezing and thawing specimens.

4. Specimens should be packaged using the triple packaging system detailed below[18]:
   - 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 are. 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[17]. Please refer to latest updates on which subnational laboratories and private hospital laboratories have available rRT-PCR tests already 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[16].

IV. Clinical presentation of patients with COVID-19 infection

1. Demographics of patients with COVID-19 infection

The following table (Table 2) describes the demographic 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[19]. 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. `

Table 2. Summary of demographics of hospitalized patients with confirmed COVID-19

Demographics	Huang, et al (N=41)[11]	Chen, et al (N=99)[13]	Wang, et al (N=138)[14]
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[20]. 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[20].

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 (14), 82% had dry cough. In the study by Chen, 90% of cases presented with more than one sign or symptom[13]. In a more recent study of 151 cases, fever remained the most common symptom[6]. Table 3 summarizes the common signs and symptoms of patients with COVID infection.

In a meta-analysis comprised of 10 studies from China (n= 50,466) (16), 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(21). 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.

Table 3. Clinical signs and symptoms of patients with COVID-19 infection

Symptom/ Sign	Huang, et al (11) (N=41)	Chen, et al (13)(N=99)	Wang, et al(14)(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 1*** below (6) shows the course of survivors vs. non-survivors

In a large meta-analysis[22] , 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%

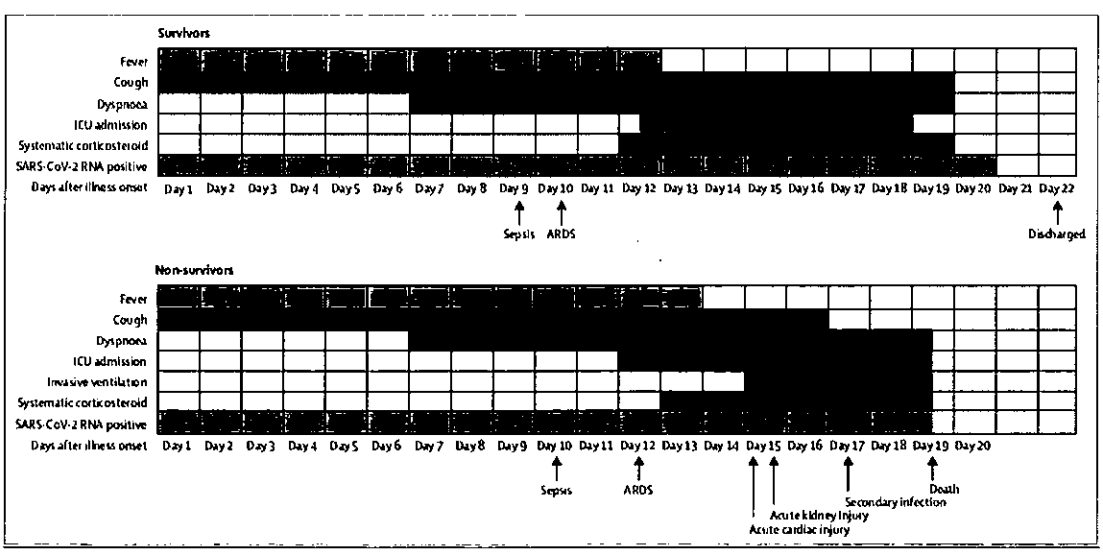


Figure 1: Clinical Course of COVID-19 Patients Among Survivors vs. Non-Survivors (6)

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[23] 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(13), 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(11), 13 (32%) patients were admitted to an ICU and six (15%) died. In the review of Wang, et. al[14], among 138 hospitalized patients, 36 (26.1%) were transferred to the ICU of which 22 (61%) developed ARDS. The mortality rate was 4.3%. To date, 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 4.

Table 4: Complications and Outcomes of Patients with Confirmed COVID-19

Outcome	Huang, et al(11) (N=41)	Chen, et al(13) (N=99)	Wang, et al(14) (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

LEGEND: 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 new DOH case definitions for notification (AO), which transitions the reporting of PUI and PUM to Suspect, Probable, and Confirmed COVID-19 cases. These definitions are consistent with the latest WHO Global Surveillance for COVID-19 disease interim guidance (as of March 20, 2020). Thus, 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.

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[a] 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. Assessed as having a high-risk pregnancy
        iv. Health 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 but 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 presence or absence of clinical signs and symptoms, who was 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.

*[a]**Contact** as defined by the WHO Global Surveillance for COVID-19 disease interim guidance (as of March 20, 2020) 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; OR

4. Other situations as indicated by local risk assessments

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 sample was taken which led to confirmation.

Table 5. Corresponding Old vs. New COVID-19 Case Definitions for Surveillance

Old Classification	New Classification
Neither PUI nor PUM	Non-COVID case
PUM	Possible case (With exposure/contact, but no symptoms)
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

B. Clinical Classification of patients with Probable or Confirmed COVID-19 infection

A. Adults (age<60) with stable or no comorbid diseases and uncomplicated upper respiratory tract infection
B. Adults (age >60) with stable or unstable co morbid diseases and pneumonia
C. Adults with severe pneumonia, severe sepsis or septic shock (manage as Community Acquired Pneumonia-High Risk (CAP-HR) based on 2020 Philippine CAP Guideline)
D. Adults with Acute Respiratory Distress Syndrome (ARDS)

Table 6. Classification of adult patients with probable or confirmed COVID-19 infection

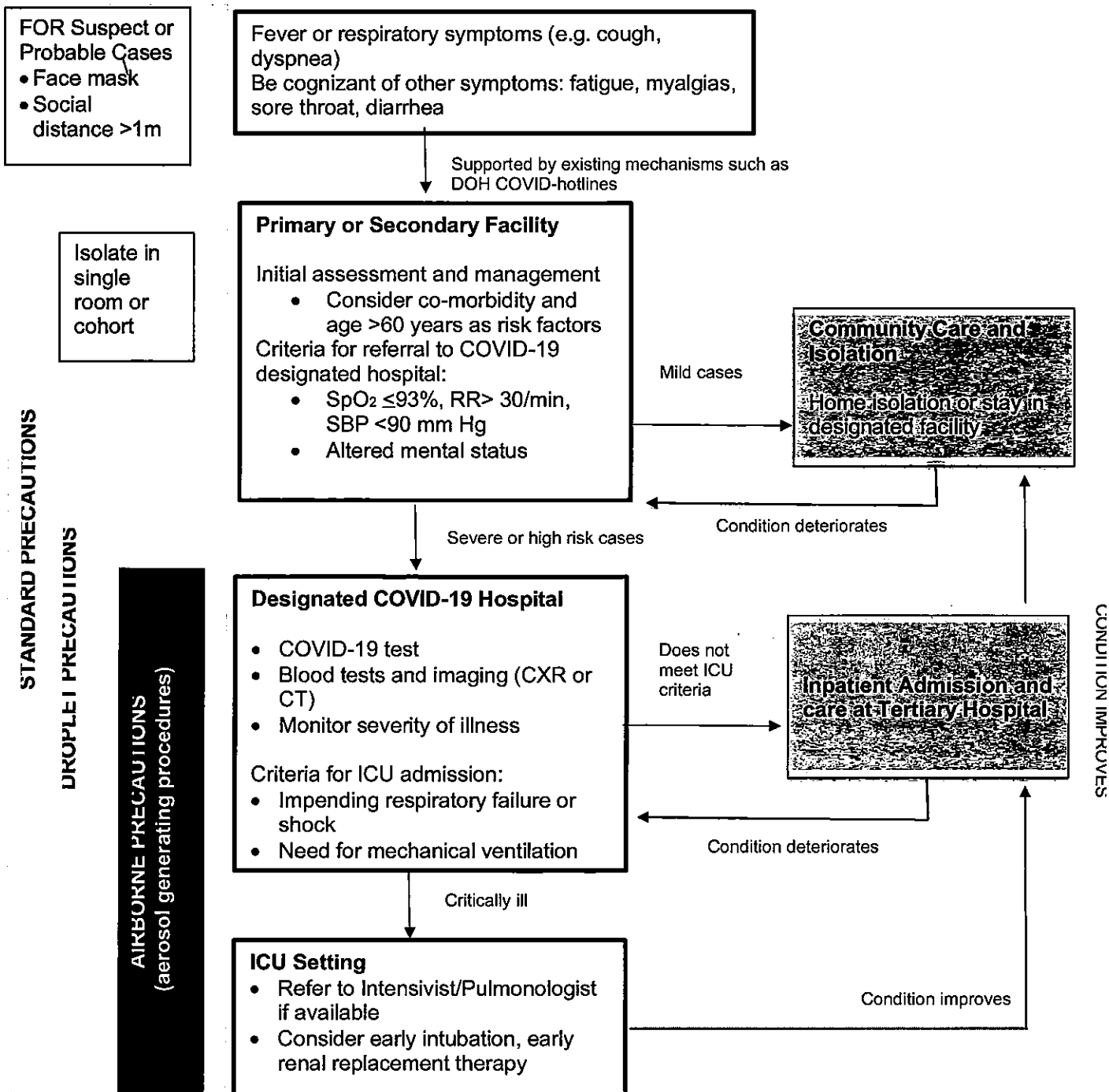
Classification	Signs and Symptoms	Recommended Diagnostics	Management
A	Adult (age <60 years) with no comorbid illness, and mild non-specific symptoms such as fever, cough, sore throat, nasal congestion, headache, muscle pain or malaise	None needed	May opt to quarantine at home for 14 days without COVID-19 testing with home quarantine instructions or send to community health facility. Give symptomatic treatment and supportive care as needed. Most cases will not require antibiotic treatment.
B	Adult (age >60 years) or young adult with stable co-morbid illness, and pneumonia (e.g. RR <30/minute, HR <125/minute, SpO2 >93% on room air)	Consider CXR, CBC, ALT, AST, creatinine CXR or CT imaging, ECG	May opt to send home young patients with stable co-morbid diseases Admit to a COVID-19 designated room/unit, and manage as CAP-Low Risk based on 2020 Philippine CAP Guidelines (Annex C)
C	Any adult with fever or severe acute respiratory infection, as follows: respiratory rate >30 breaths/minute severe respiratory distress, or SpO_2 ≤93% on room air	CBC Comprehensive metabolic panel Ferritin, LDH, procalcitonin, CRP, INR/PT, D dimer, lactate CXR or CT imaging Sputum GS/CS, blood cultures, as appropriate ABG	Manage as CAP-Moderate Risk based on 2020 Philippine CAP Guidelines (Annex C)
	Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction presenting as follows: 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		Manage as CAP-High Risk based on 2020 Philippine CAP Guidelines (Annex C)

	Septic Shock: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level >2 mmol/L		Manage as CAP-High Risk based on 2020 Philippine CAP Guidelines
D	Within 1 week of known clinical insult 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	ABG Ferritin, LDH, Procalcitonin, CRP, INR/PT, D dimer, lactate Repeat CXR or CT imaging ETA GS/CS, blood cultures, as appropriate	Consider ARDS – management will depend on classification of ARDS. See Section VIII.

Table 7. Risk stratification for Community Acquired Pneumonia for Adults (Adapted from PSMID CAP 2020 Guidelines)

PARAMETER	Low Risk	Moderate Risk	High Risk
Vital Signs	Stable	Unstable	
Respiratory rate	< 30/minute	≥ 30/minute	
Pulse rate	<125/minute	≥125/minute	
Systolic blood pressure	> 90 mmHg	< 90 mmHg	
Diastolic blood pressure	> 60 mmHg	≤ 60 mmHg	
Temperature	> 36°C or < 40°C	≤ 36°C or ≥ 40°C	
Others			
Altered mental state of acute onset	Absent	Present	Present
With suspected aspiration	No	Yes	Yes
Co-morbid condition	None or stable co-morbid conditions	Unstable or decompensated Uncontrolled diabetes mellitus Active malignancies Neurologic disease in evolution Congestive heart failure Class II-IV Unstable coronary artery disease Renal failure on dialysis Uncompensated COPD Decompensated liver disease	
Severe Sepsis and Septic shock	Absent	Absent	Present/Absent
Need for mechanical ventilator	No	No	No/Yes

Figure 2. 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/or respiratory distress, hypoxemia, or shock and target SpO_2 >94%.**
    - Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO_2 ≥93% during resuscitation. Use face mask with reservoir bag at 10-15 L/min for critically ill patients. For acute hypoxemic respiratory failure despite conventional oxygen therapy, use high-flow nasal cannula (HFNC), if available.
    - Target SpO_2 ≥90% in non-pregnant adults, once stable.
    - 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).
- Regularly assess the need for intubation and mechanical ventilation. Early intubation is recommended for patients with COVID-19. A trained and experienced provider should perform endotracheal intubation under airborne precaution.
- 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 ventilation.
- 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.
- Give oseltamivir 75 mg per tab BID for adults for 5 to 10 days for patients who are confirmed to have influenza A or B infection.
- Streamline antimicrobial treatment when microbiologic study results become available.
- Do NOT routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.
    - There is insufficient evidence to support the use of steroids in the management of patients with confirmed or suspected COVID-19 infection with acute lung injury and ARDS. Use of steroids may provide little benefit and cause more harm among these patients[9].
- Closely monitor patients with pneumonia for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately.
- Identify and properly manage other co-morbidities adequately.

VII. Management of Severe Sepsis or Septic Shock [24]

(Adapted from PSMID 2020 Sepsis Guidelines)

- 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. Please refer to 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 of recognition.
    - 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 after initial fluid resuscitation within the first hour. The initial blood pressure target is MAP ≥65 mmHg in adults. Use of vasopressors should not be delayed.
- 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.
- If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.

VIII. Management of Acute Respiratory Distress Syndrome (ARDS) [25]

Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy.

1. **Signs and symptoms**

Onset: new or worsening respiratory symptoms within one week of known clinical insult
Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules
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

2. **Classification of ARDS based on oxygenation among adults:**

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

3. **Management of ARDS**
   - Admit the patient to the ICU.
   - Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy.
   - Hypoxemic patients without ARDS should be monitored closely in an ICU setting for clinical deterioration and need for invasive mechanical ventilation. In these patients, high flow nasal oxygen (HFNO) therapy or non-invasive ventilation IS NOT beneficial, and early intubation/ mechanical ventilation should be considered. For those with advance directives, non-rebreather masks may be an option.
   - Manage ARDS if present. Referral to the appropriate specialists (e.g. Pulmonologist and/or Intensivist) is highly recommended.
   - Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions.
   - 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
     - In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested.
   - 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.
   - Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.
     - This is a strong guideline recommendation; the main effect is to shorten the duration of ventilation. (PSMID Sepsis Guidelines 2020)
   - In patients with moderate-severe ARDS (PaO_2/FiO_2 <150), neuromuscular blockade by continuous infusion should not be routinely used.
   - 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.

- Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, de- recruitment and atelectasis.
- Minimize nebulization as it can also cause de-recruitment. Keep the ventilator humidified at all times. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).
- A list of complications related to critical illness and how to prevent them is listed in Table 9.

IX. Investigational Drugs for Treatment of COVID Pneumonia

The use of specific therapy for COVID-19 is currently limited to in-vitro studies and case series, although several randomized controlled trials are currently underway (http://www.chictr.org.cn/enIndex.aspx). Of the drugs under investigation, the following anti-infectives are available for off-label use (hydroxychloroquine, chloroquine, lopinavir/ ritonavir, tocilizumab), or may be available for compassionate use (remdesivir).

A. Remdesivir: (RD, formerly GS-5734) is a prodrug of a modified adenine nucleoside analog GS-441524. RD undergoes efficient metabolic conversion in cells and tissues to active nucleoside triphosphate metabolite that inhibits viral RNA polymerases, but not host RNA or DNA polymerases. It has been recently recognized as a promising antiviral drug against a wide array of RNA virus (including SARS/MERS-CoV5) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection(26). RD is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination(27). Holshue *et al.* reported that RD yielded promising results in the treatment of a patient with COVID-19 in the United States[28]. To evaluate the efficacy and safety of the drug in patients with COVID-19, two randomized, placebo-controlled, double-blind, multicenter, phase III clinical trials were launched last February 2020 in China [https://clinicaltrials.gov/ct2/show/NCT04252664; https://clinicaltrials.gov/ct2/ show/NCT04257656 (accessed March 18, 2020)]. In both studies, patients in the experimental group receive a former RD regimen used in the randomized clinical trial of Ebola virus disease; that is, a loading dose of 200 mg of RD on day 1 and a subsequent dose of 100 mg once daily, as maintenance dose, for 9 consecutive days via intravenous infusion in addition to routine treatment [29]. Patients in the control group receive routine treatment and the same dose of a placebo. The trials are expected to conclude by the end of April to May 2020.

B. Chloroquine or hydroxychloroquine (CQ or HCQ): CQ is a 4-aminochloroquine used mainly as an anti-parasitic agent. HCQ differs from CQ only by hydroxylation at the end of the side chain and they have the same mechanism of action. However, the clinical safety profile of hydroxychloroquine is better than that of chloroquine (during long-term use), allows higher daily dose(30) and has fewer side effects (31).

CQ has been shown to inhibit the infection of influenza type A and B and adenovirus in target cells (32). In early in-vitro studies, CQ was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-

cytotoxic concentration (CC50) greater than 100 μM [33]. A number of subsequent clinical trials have been quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19-associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo(34). Results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus- negative conversion, and shortening the disease course according to the news briefing (unpublished data). Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients. Given these findings, experts have agreed that chloroquine phosphate may have potent activity against COVID-19. The drug is now recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China. In a systematic review of 6 articles (35) on the efficacy and safety of chloroquine for the treatment of COVID-19, the authors found pre-clinical evidence of effectiveness and evidence of safety from long-term clinical use for other indications as bases to justify clinical research on CQ use in patients with COVID-19. The Italian Society of Infectious and Tropical Disease guidelines recommended a suggested target population of patients with mild respiratory symptoms and comorbidities as well as patients with severe respiratory failure.

In a recent non-randomized study of confirmed COVID-19 patients, 20 patients given HCQ 200 mg/tab 3 tabs daily showed a significant reduction of the viral carriage at D6-post inclusion compared to 16 controls, and much lower average carrying duration than reported of untreated patients in the literature [36]. Notably, 6 patients treated with hydroxychloroquine and azithromycin combination were virologically cured compared with 57.1% in patients treated with hydroxychloroquine only, and 12.5% in the control group ($p<0.001$).

C. ***Lopinavir-ritonavir:*** Lopinavir/ritonavir (LPV/r) is a protease inhibitor, available only as combination pill. This medication has been used to treat adults and children over 14 days of age who are infected with the human immunodeficiency virus type 1 (HIV-1). Chu *et al.* (37) found that LPV/r has anti-SARS-CoV activity *in vitro* and in clinical studies. 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, 37, 38), and clinical trials are also underway.

To evaluate the efficacy and safety of oral lopinavir–ritonavir for SARS-CoV-2 infection, a randomized, controlled, open-label trial, LOTUS China (Lopinavir Trial for Suppression of SARS-Cov-2 in China), in adult patients hospitalized with severe Covid-19 was conducted from January 18, 2020, through February 3, 2020(39). In the intention-to-treat population, lopinavir–ritonavir treatment within 12 days after the onset of symptoms was associated with shorter time to clinical improvement but beyond 12 days no difference in clinical improvement was seen. Time to clinical deterioration did not differ significantly between the LPV/r group and the control group. Mortality did not also differ significantly between the 2 groups but respiratory failure or ARDS was significantly higher in the standard of care group compared to the LPV/r group.

D. ***Tocilizumab*** is a recombinant humanized anti-human IL-6 receptor monoclonal antibody and can specifically bind sIL-6R and mIL-6R and inhibit signal transduction. It is currently used

mainly for rheumatoid arthritis (40). 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 (40-42). Its use for SARS-CoV2 remains investigational, but in an observational retrospective study (43), a single infusion of Tocilizumab given to severely or critically ill COVID-19 patients resulted in prompt improvement in clinical, inflammatory and radiologic markers.

E. ***Other drugs:*** There is insufficient evidence to recommend the use of Vitamin C and zinc as adjunctive treatment for COVID-19. (See Annex B and C).

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.

Based on this limited evidence and expert opinion, hydroxychloroquine (HCQ) or chloroquine (CQ) may be considered for use in hospitalized, probable or confirmed COVID-19 cases with moderate to high-risk pneumonia. If with contraindications to the use of HCQ or CQ, consider using lopinavir/ritonavir. Please see Figure 3a and b and Table 8.

Each patient must sign an informed consent prior to use of these investigational drugs, with the attending physician discussing the benefits based on currently available evidence, and potential adverse drug reactions.

Figure 3a: Management Algorithm for Probable or Confirmed COVID-19 Pneumonia (Remdesivir not yet locally available)

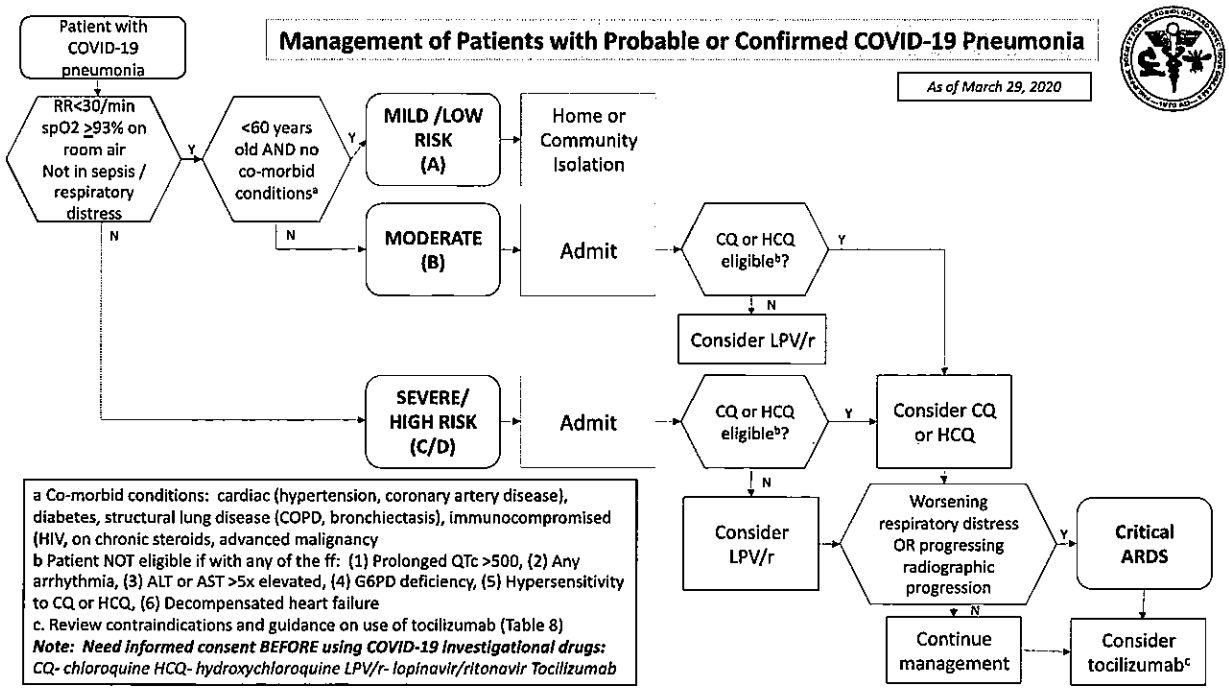


Figure 3b. Algorithm for Use of Investigational Drugs for COVID-19 (if Remdesivir available)

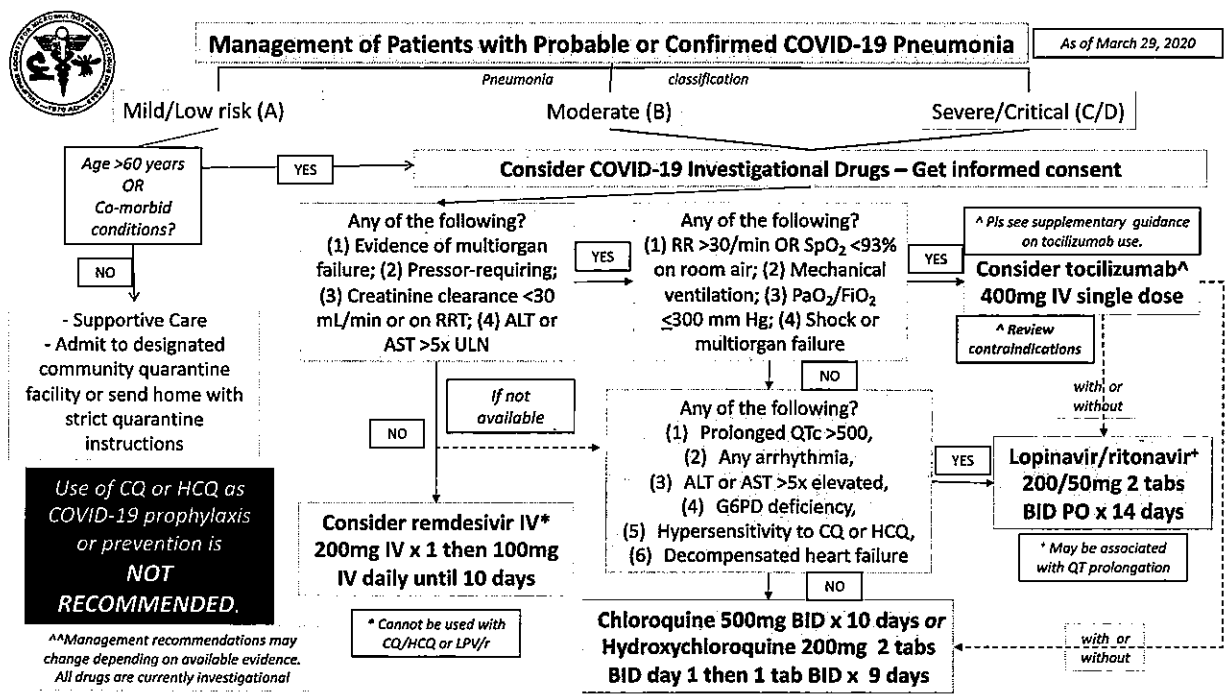


Table 8: Guidance on the Use of Tocilizumab

INDICATIONS		CONTRAINDICATIONS	MONITORING
May use a combination of clinical and diagnostic criteria		**ABSOLUTE**	**BEFORE STARTING***
Clinical Criteria(44)	***Diagnostic Criteria (12) ^***		
Severe	T> 38.4°C Hepato- or splenomegaly Any bicytopenia Triglycerides between >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 Active tuberculosis	Screen for TB, Hepatitis B (HBsAg, anti-HBc [core] IgM/IgG)
RR >30 SpO2< 93 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

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

A. Adverse Drug Reactions(45-48)

1. **Remdesivir** – The ADRs of RD remain largely unknown at this time. In a randomized clinical trial (26), patients on RD were more likely to develop hypotension.

2. **Chloroquine or Hydroxychloroquine** – Both have a narrow therapeutic range with many side effects. These include ophthalmic complications (retinopathy, 7.5%), neurologic complications (dystonia, dyskinesia), cardiac (arrhythmias), hematologic (hemolysis, aplastic anemia, thrombocytopenia), hearing loss, hypoglycemia, and others. It also has many drug-drug interactions.

3. **Lopinavir-ritonavir** – LPV/r is generally well-tolerated but may be associated with gastrointestinal side effects such as nausea (10.3%), vomiting (6.8%), and diarrhea (19.5%). Other common side effects include headache, including migraine (6.3%). Serious side effects are rare but can include AV block and prolonged QTc interval (0.1%), pancreatitis (1.7%), elevation in ALT/AST with long term use (10%).

   In a prospective, single-center cross-sectional study of HIV-infected patients, anti-HIV treatment, in particular protease inhibitor (P=0.99), was not associated with QTc prolongation; the only HIV variable independently associated with QTc prolongation was the duration of infection (P=0.023).

Prolonged QTc interval among the HIV+ patients in this study was associated with other factors commonly known to prolong QT (i.e. incomplete bundle branch block, ventricular hypertrophy, signs of ischemic cardiopathy). (Charbit, et al., 2009)

4. **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.

B. Monitoring

1. **Remdesivir** – Clinical monitoring is unknown.

2. **Chloroquine or hydroxychloroquine** –

2.1. Monitor QTc interval by performing a 12-lead electrocardiogram (ECG) at baseline, on Day 5 (D5) and on D10. If QTc >500 ms, decrease drug dose or discontinue.
2.2. Do CBC every 48 hours and evaluate for cytopenia.
2.3. Ask patients about changes in vision on a daily basis.
2.4. Work closely with pharmacy and evaluate for drug-drug interactions (e.g. Concomitant use of azithromycin and fluoroquinolones are prohibited)

3. **Lopinavir/ritonavir** –

3.1. Work closely with pharmacy and evaluate for drug-drug interactions since LPV/r is a potent CYP4503A4 inhibitor.
3.2. Do baseline CBC, glucose, and ALT/AST then monitor periodically.
3.3. Monitor for loose stool or diarrhea.
3.4. Monitor QTC especially if used with other QTc prolonging drugs.

4. Tocilizumab

4.1 Evaluate for latent/active TB prior to initiation.
4.2 Check baseline CBC, and ALT/AST and monitor periodically.
4.3 Check baseline lipid panel and monitor periodically
4.4 Do Hepatitis B and TB screening at the minimum.

XI. Dosing Regimen and Duration of Investigational Drugs ^

Table 9: Dosing Regimen and Duration of Investigational Drugs

REMDESIVIR	CHLOROQUINE (CQ) or HYDROXYCHLOROQUINE (HCQ)	TOCILIZUMAB	LOPINAVIR / RITONAVIR
= 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 10 days, but dosing may be continued for an additional 4 days at 100 mg IV once daily if COVID-19 remains detectable at day 10 of treatment.	**CQ** - 500mg/tab 1-tab BID PO for 10 days **HCQ** - 200mg/tab 2 tabs BID day 1 then 1-tab BID x 9 days **OR** 200mg/tab 3 tabs daily for 10 days	4-8mg/kg single dose with recommended dose of 400mg IV diluted in 0.9 NS to 100mL, given as a 2-hour infusion A single extra dose may be given after 12 hours at the discretion of the provider (49).	200mg/50mg-tab 2 tabs BID for 14 days

^ *The optimal doses required for treatment of COVID-19 is largely unknown.*

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. See Annex A.

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 care of should be in place (example: rotation of health teams, psychosocial support, buddy system to ensure that PPEs are properly worn, proper management of HCW exposures, access to testing)**

XIII. Prevention of Complications

Implement the following interventions to minimize complications associated with critical illness.

Table 9: Interventions for Prevention of Complications(25)

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 (if with available test kits)**

    a. Submit NPS/OPS and lower respiratory tract specimens (if possible) at 14 days from the first positive COVID-19 test, or once patient is afebrile for 72 hours, whichever is longer.

    b. If still positive, recollect NPS/OPS and lower respiratory tract specimens (if test kits are available) for COVID-19 testing after 14 days.

    c. If test kits are not available, patients may be sent home once asymptomatic and clinically stable. Advice the patient to stay on home quarantine for another 14 days and repeat the test once kits are available.

2. **Repeat testing after an initial negative COVID-19 test**

    Repeat testing for patients with an initial negative COVID-19 test result is subject to availability of test kits and may 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 discharge

1. Criteria for discharge of COVID-19 Probable or Suspect Case

   A COVID-19 Probable or Suspect Case may be discharged after the initial COVID-19 test is negative AND any of the following conditions are met:

   - There is clinical improvement.
   - There is no other indication for admission.
   - An alternative diagnosis is available.
   - The probability of COVID-19 has been ruled out.

2. Criteria for discharge of patients with confirmed COVID-19 infection

   Patients who have clinically recovered (with resolution of symptoms) may be discharged from the hospital after a single negative test; if kits are in abundant supply, two consecutive negative tests 24 hours apart for SARS-CoV2 is preferred or at least one negative test prior to discharge.

   If it is not possible to repeat the test, patients can be discharged upon discretion of the healthcare team, but they should remain under strict home quarantine for 14 more days until after resolution of their last symptom. They should be tested at least once after this 14-day period, if the testing kit is available. Either RT-PCR or a rapid antibody test can be done.

   The IgG antibody can be used as an adjunct test to clear quarantined patients who remain asymptomatic at 14 days post discharge. The presence of antibodies typically indicates viral clearance. If IgG is positive, the patient can be released from self-quarantine. If IgG is negative, a repeat RT-PCR should be performed

   Resolution of symptoms may include the following:
   - The body temperature returns to normal> 3 days;
   - Respiratory symptoms have improved significantly;
   - Chest radiograph shows significant improvement

3. Health management of discharged patients
   - For discharged patients, close follow-up is still required.
   - When a patient is discharged from the hospital, his place of residence and address should be recorded.
   - Patients should rest at home for 2 weeks after leaving the hospital, avoid activities in public places, and must wear masks when going out.
   - Monitor the patient's temperature and health status for 2 weeks.
   - 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 treatment. This should be reported to the corresponding surveillance units of the Department of Health.

a. The discharge from hospital of mild cases – if clinically appropriate – may be considered, provided that they are placed into home care or another type of community care. After discharge, 14 days of further isolation with regular health monitoring (e.g. follow-up visits, phone calls) can be considered, provided the patient's home is equipped for patient isolation and the patients take all necessary precautions (e.g. single room with good ventilation, face-mask wear, reduced close contact with family members, separate meals, good hand sanitation, no outdoor activities) in order to protect family members and the community from infection and further spread of SARS-CoV-2.

b. Health management for asymptomatic COVID-19 positive contacts of confirmed cases
   - They should remain under home quarantine for 14 days from the time they tested positive for COVID-19.
   - Should they develop fever or respiratory symptoms within this 14-day self-quarantine period, they should seek consultation for evaluation and repeat COVID-14 testing, as deemed appropriate and best done in consultation with an infectious disease specialist.

XVI. 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 on 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.

Annex A. Rapid review of Hydroxychloroquine for Prophylaxis

Should hydroxychloroquine be used as prophylaxis for the COVID-19 virus?
This is a rapid review on available evidences regarding the use of hydroxychloroquine as prophylaxis to COVID-19. This may change as new evidences emerges.

Background
Hydroxychloroquine (HCQ) is an antimalarial drug and a Disease Modifying Anti-Rheumatic Drug. Various clinical trials on HCQ as treatment for COVID-19 are currently on-going. (50)

Search of Literature
The following electronic databases were searched for evidences: Medline, CENTRAL, ClinicalTrial.gov and Chinese Clinical Trial Registry.

Evidence
Currently there are no published clinical trials on the use of hydroxychloroquine as prevention for COVID-19. There are at least four ongoing clinical trials on the effectiveness of HCQ as a prophylaxis for COVID-19. See Table 1.

Clinical Trial Identifier	Official Title	Methodology	Estimated Date of Start	Estimated Date of Completion
NCT04318015	Chemoprophylaxis With Hydroxychloroquine in Healthcare Personnel in Contact With COVID-19 Patients: A Randomized Controlled Trial (PHYDRA Trial)	Triple blinded, randomized controlled trial	April 1, 2020	December 31,2020
NCT04308668	Post-exposure Prophylaxis for SARS-Coronavirus-2	Triple blinded, randomized controlled trial	March 17,2020	May 2021
NCT04304053	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (HCQ4COV19)	Cluster-randomized clinical trial	March 18, 2020	June 15, 2020
ChiCTR2000031174	Effectiveness and safety of hydroxychloroquine sulfate in the preventive treatment of novel coronavirus pneumonia (COVID-19)	Double blinded, randomized controlled clinical trial	March 23,2020	September 30, 2020

An in-vitro study of chloroquine, a chemically related drug to hydroxychloroquine, was shown to inhibit the entry of SARS-COV2 into Vero cells by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.(14) This finding was supported by

another in-vitro study comparing chloroquine and hydroxychloroquine.

Conclusion

At this time, there is insufficient evidence to support the use of hydroxychloroquine as pre-exposure or post-exposure prophylaxis for COVID-19. Results of ongoing clinical trials are needed.

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Prepared by: Ian Theodore Cabaluna, MD, Diploma in Clinical Epidemiology
March 22, 2020

Annex B. Rapid Review of Zinc as an adjunct in the treatment of COVID-19

KEY FINDINGS

There is no current clinical evidence that zinc or zinc supplements are effective adjunctive treatment for Covid-19.

BACKGROUND

Zinc is widely used as a supplement and functions as a component of various enzymes responsible for the structural integrity of proteins and regulation of gene expression.[1] It is the latter's function that seemed to be the focus of interest in the Covid-19 pandemic.

An in vitro study by te Velthuis (2010)[2] showed that increasing the intracellular Zn^{2+} and pyrithione as ionophores effectively inhibit the replication of SARS-coronavirus (SARS CoV) by inhibiting the RNA-dependent RNA polymerase elongation. This is the only study that has linked the elemental zinc to the coronavirus to date.

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METHODS

LITERATURE SEARCH METHODS

A comprehensive search of two electronic databases (CENTRAL, Medline) and three clinical trial registries (ClinicalTrials.gov, Chinese Clinical Trial Registry (ChiCTR), EU Clinical Trials Register) was conducted. UptoDate was also searched for references. ChinaXiv.org was also searched for any relevant studies awaiting peer-review. (See Table 1)

SELECTION CRITERIA AND METHODS

P all ages, male and female diagnosed with COVID-19 /SARS-COV 2

I zinc or zinc supplements

C placebo or active drug
O therapeutic relief/resolution
M published research and reviews including, but not limited to, RCTs, SRs, case series, case reports, descriptive studies

INCLUSION CRITERIA
To be included in the search are randomized clinical trials, case reports, case series, published research and reviews, for all ages, male and female, on Covid-19 and the use of zinc, zinc compounds or zinc supplements as sole or combined, therapeutic or adjunctive treatment, for mild to moderate stages of the disease. Included are studies done in English and other languages (if English translation is available). Also included are published researches on previous coronavirus infections like SARS and MERS as part of indirect evidence.

EXCLUSION CRITERIA
In vitro studies and animal studies.

SUMMARY OF EVIDENCE

There were no clinical studies that assessed the effectiveness of zinc, zinc compounds or zinc supplements, either as a direct or adjunctive treatment for COVID-19.

Indirect evidence can be derived from 2 systematic reviews. Lassi et al (2016)[3] reviewed 6 RCTs on elemental zinc versus placebo administered to children 2 to 59 months of age for at least 3 months. Outcome surveillance was observed for at least 4 weeks. When the clinical symptoms of pneumonia were used for diagnosis, there was no significant difference between zinc and placebo (RR 0.95,95% CI (0.86-1.06)), 4 trials/ 1932 children. When chest examination or chest x-ray was used as basis, there was statistical significance at 21% reduction in pneumonia incidence (RR 0.79, 95% CI (0.71-0.88), 4 trials/3261 children. The studies were from low- to middle-income countries where zinc deficiency is common. However, the quality of evidence for both incidence and prevalence of pneumonia was low.

The second systematic review was done by Singh (2013)[4] on zinc and and its effectiveness in reducing the incidence, severity and duration of common cold symptoms, usually due to rhinovirus. 18 trials with participants aged 1 to 65 years were included in both therapeutic (1387 participants) and preventive (394) trials. Therapy was initiated within 3 days of developing the common cold symptoms while prophylaxis was done for at least 5 months during the entire cold season. Pooled results showed reduction in the duration, but not severity of the cold symptoms, in high doses. Incidence was also reduced. However, the quality of evidence was low to very low due to heterogeneity (different interventions, doses, population characteristics, co-morbidities), publication bias, allocation concealment.

RECOMMENDATIONS BY WHO, CDC

According to WHO, there are no currently approved guidelines on the use of zinc and stated that further research is needed before any recommendations can be made.

There were no recommendations from CDC on zinc as an adjunctive treatment.

Table 1. LITERATURE SEARCH

Database	Search strategy	Date of Search	Results
Medline	((2019 novel coronavirus disease OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR coronavirus disease 2019 OR coronavirus disease-19 OR coronavirus* OR coronovirus* OR coronavirus Infections OR Wuhan coronavirus OR 2019-nCoV OR COVID-19 OR CORVID-19 OR wn co OR novel coronavirus OR new coronavirus OR 2019 novel OR new coronavirus OR ncov OR SARS-CoV-2 OR SARSCov19 OR ncov* wuhan)) AND ("zinc"[MeSH Terms] OR zinc[Text Word])	March 29, 2020 02:02:07 GMT +8	0
CENTRAL	((zinc):ti,ab,kw OR (zinc acetate):ti,ab,kw OR (zinc supplement):ti,ab,kw AND (COVID 19 OR COVID-19 OR NCOV OR novel coronavirus OR coronavirus OR SARS COV 2 OR 2019 NCOV)	March 29, 2020 14:12:06 GMT+8	1
ClinicalTrial.gov	Zinc OR zinc supplement	March 29, 2020 14:24:25 GMT+8	0
UptoDate	Zinc supplemments and Covid-19	March 29,2020 14:37 GMT+8	1
Chinese Clinical Trial Registry	Zinc	March 29, 2020 14:31 GMT+8	0
EU Clinical Trials Register	Zinc or zinc supplement	March 29, 2020 14:20:00 GMT+8	0
ChinaXiv	Zinc	March 29, 2020 14:33 GMT+8	0

TABLE 2. SUMMARY TABLE

Author, Year	Methodology	P	I	O
Lassi, 2016	Systematic Review of 6 studies	5193 Children 2 months to 59 months	Elemental zinc vs placebo	Incidence and prevalence of pneumonia
Singh, 2013	Systematic review of 18 RCTs	1387 participants for the therapeutic trials and 394 in the preventive trials, aged 1 to 65 years	Zinc supplements vs placebo	Reduction in the duration, severity and incidence of the common cold

Prepared by: Gina S Eubanas, MD, FPDS, Dip (Clin Epi) March 28, 2020

Annex C: Rapid Review on the Use of Vitamin C for COVID-19 Patients

Clinical Question

Among adult patients under investigation or positive for COVID-19, how effective is intravenous vitamin C + standard of care versus standard of care alone, in preventing mortality and shortening length of disease course?

Key Findings

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. The mortality outcome in CITRIS-ALI may not be clinically robust and may not statistically persist in a larger setting.

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Fowler, AA III et al. 2019. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure. The CITRIS-ALI Randomized Clinical Trial.

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Methods

Literature Search Methods

A primary search of Pubmed was done using the following strategy (last carried out March 29, 2020):
(("Ascorbic Acid"[Mesh]) OR ("ascorbic acid") OR (ascorbate) OR ("vitamin C")) AND (("COVID-19"[Supplementary Concept]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR ("sars-cov-2") OR ("covid-19") OR ("ncov"))
A secondary search for indirect evidence in Pubmed was also done with the following strategy:
(("Ascorbic Acid"[Mesh]) OR ("ascorbic acid") OR (ascorbate) OR ("vitamin C")) AND (("Virus Diseases"[Mesh]) OR ("Influenza, Human"[Mesh]) OR (influenza) OR (cold))
UpToDate was also searched for pertinent information on vitamin C in COVID, particularly for cited Guidelines from different societies or localities.

Google search was also done to check for other sources of information, including gray literature, and society statements. Trial registries were also searched.

Selection Criteria and Methods

Randomized controlled trials or systematic reviews/meta-analyses from year 2000 onwards, were included. Only those that studied intravenous vitamin C and COVID-19 were included, and if unavailable, those studying viral diseases, particularly influenza or colds. Only human studies were included. Two reviewers were involved in the selection process and disagreements were resolved by consensus.

Inclusion criteria (PICOM)

P: adult patients suspected of, or positive for COVID-19
I: intravenous vitamin C + standard of care
C: standard of care alone
O: preventing mortality, shortening length of disease course
M: randomized controlled trials, systematic reviews/meta-analysis

Exclusion Criteria

Non-human studies
Observational studies
Literary articles (e.g. blogs)
Studies older than 2000
Academic reviews

Critical Appraisal of included studies

Included articles were appraised using accepted processes evaluating directness, validity, and applicability.

Summary of Evidence

Summary of Findings

There are no completed clinical trials or systematic reviews/meta-analyses studying the efficacy of intravenous vitamin C in COVID-19.

Currently, there are 4 trials (3 already recruiting, 1 to start recruiting) registered in clinicaltrials.gov studying intravenous vitamin C in COVID-19.

Two clinical trials studied the effect of vitamin C among septic patients:

The CITRIS-ALI trial was a randomized, double-blind, placebo-controlled, multicenter trial conducted in 7 medical intensive care units in the United States, enrolling patients (N = 167) with sepsis and ARDS present for less than 24 hours. Patients were randomly assigned to receive intravenous infusion of vitamin C or every 6 hours for 96 hours. Vitamin C did not improve the primary outcome of organ dysfunction scores or alter markers of inflammation and vascular injury. However, mortality, which was one of the 46 pre-specified secondary endpoints, was significantly lower with vitamin C. No unexpected study-related adverse events occurred during the trial.

The VITAMINS trial was a multicenter, open-label, randomized clinical trial conducted in 10 intensive care units in Australia, New Zealand, and Brazil that recruited 216 patients fulfilling the Sepsis-3 definition of septic shock. Patients were randomized to control of hydrocortisone alone, versus hydrocortisone + thiamine + intravenous vitamin C. Treatment with intravenous vitamin C, hydrocortisone, and thiamine, compared with intravenous hydrocortisone alone, did not significantly improve the duration of time alive and free of vasopressor administration over 7 days. Adverse events were reported for 2 patients (2 events,

fluid overload and hyperglycemia) in the intervention group and 1 patient (1 event, gastrointestinal bleeding) in the control group. No SAEs or SUSARs reported.
Finally, a Cochrane meta-analysis on Vitamin C for the treatment and prevention of the common cold was done in 2013. Regular ingestion of vitamin C did not affect incidence of common colds in the ordinary population (n=11306, 29 trials), but had a modest, consistent effect in reducing duration (31 study comparisons, 9745 common cold episodes). In 5 trials with 598 participants exposed to short periods of extreme physical stress (including marathon runners and skiers), vitamin C reduced by half the risk for common colds.

b. Summary of Guidelines
There are no guidelines recommending the use of vitamin C in the management of COVID-19.
The Therapeutic Goods Administration of the Australian Government Department of Health had issued guidance stating "there is no robust scientific evidence to support the usage of this vitamin in the management of COVID-19".

Conclusions and implications for decision
There is no direct evidence available at this time on the efficacy of intravenous vitamin C in preventing mortality or shortening disease course among adults suspected of, or positive for COVID-19.

Indirect evidence for intravenous vitamin C in sepsis and ARDS shows no significant benefit. However, the studies are small and further studies may be attempted to elucidate the effects of vitamin C, especially on hard outcomes like mortality and length of disease course.

The modest benefits of regular vitamin C supplementation can only be applied to common colds. The findings of the Cochrane meta-analysis cannot be applied to other viral illness, especially moderate to severe ones, since the pathophysiology of the diseases are clearly different, and interaction with other factors like comorbidities may further modify the effect of the intervention.

The supposed benefit on mortality (one of many secondary outcomes) in the CITRIS-ALI trial may not be clinically robust and not representative of the true effect of vitamin C. It may not statistically persist in a larger setting.

The trials have not reported any adverse event, and the decision to use intravenous vitamin C should also take this into account.

The decision to use intravenous vitamin C in suspected or proven positive COVID-19 patients is empiric. This should be discussed with the patient, family and within the healthcare team, including the need for an informed consent to include vitamin C in the overall patient management.

Declaration of Conflict of Interests
None

Appendix 1. Characteristics of included studies, trial registries
No primary studies available

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting NEW	Use of Ascorbic Acid in Patients With COVID 19	• Hospitalized Patients With Covid-19 Pneumonia	• Dietary Supplement: Vitamin C	• A.R.N.A.S. Civico - Di Cristina - Benfratelli Palermo, Italy
2	☐	Recruiting	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	• Vitamin C • Pneumonia, Viral • Pneumonia, Ventilator-Associated	• Drug: VC • Drug: Sterile Water for Injection	• Zhongnan Hospital of Wuhan University Wuhan, Hubei, China
3	☐	Recruiting	Lessening Organ Dysfunction With VITamin C	• Sepsis • Vitamin C • Intensive Care Unit • (and 3 more...)	• Drug: Vitamin C • Other: Control	• Research Center of the CHUS Sherbrooke, Quebec, Canada
4	☐	Not yet recruiting NEW	Anti-inflammatory/Antioxidant Oral Nutrition Supplementation in COVID-19	• COVID-19	• Dietary Supplement: oral nutrition supplement (ONS) enriched in eicosapentaenoic acid, gamma-linolenic acid and antioxidants • Dietary Supplement: isocaloric/isonutrigenous ONS	

Appendix 2. Critical Appraisal of Included Primary Studies

No primary studies available.

Prepared by: Marc Evans M. Abat, MD, FPCP, FPCGM (March 29, 2020)
Internist - Geriatrician
Consultant Director, Center for Healthy Aging, The Medical City
Clinical Associate Professor, Section of Adult Medicine, Philippine General Hospital

Annex D. 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	

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Rapid Review: Hydroxychloroquine and azithromycin

I. Research Question:

Should we use hydroxychloroquine (HCQ) and azithromycin to improve clinical outcome in patients with CoVID-19?

This is a rapid review on available evidences regarding the use hydroxychloroquine (HCQ) and azithromycin to improve clinical outcomes in patients with CoVID-19. This may change as new evidences emerge.

II. Key Findings

There was one open-label nonrandomized trial by Gautret et al. which showed a trend towards benefit of the use of hydroxychloroquine and axithromycin together, for the purpose of virologic cure and rendering patients non-contagious. This study, however, had a very small sample size and did not look at clinical outcomes as an endpoint.

An extension study, designed as a descriptive observational one, used the combination on 80 patients (six of whom were from the original study). There was clinical improvement (at the time of writing of the study) in 83% of patients, who were discharged from the infectious disease ward. Ninety-three percent (93%) of the patients were negative for virus on Day 8 of treatment; 0% were contagious on Day 12. While the findings are encouraging, no conclusions can be drawn from the study due to the absence of a comparison group.

III. References

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Gautret P, Lagier J, Parola P, Hoang V, Meddeb, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study
Running title: Hydroxychloroquine-Azithromycin and COVID-19

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https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management

IV. Methods

The following electronic databases were searched for studies: UpToDate, Medline, CENTRAL, PROSPERO, WHO International Clinical Trials Registry Platform, ISRCTN registry, ClinicalTrial.gov and the Chinese Clinical Trial Registry.

On PubMed, the search strategy used included the terms ((((CoVID-19) OR novel coronavirus infection) OR nCoV)) AND ((((((hydroxychloroquine plus azithromycin) OR (hydroxychloroquine and azithromycin)) OR hydroxychloroquine) OR azithromycin) OR (HCQ and azithromycin)) OR HCQ with azithromycin).

The terms "hydroxychloroquine," "azithromycin," "hydroxychloroquine and azithromycin," "COVID-19" were used for the search in the other electronic databases.

The PICOM table for studies for inclusion appears in Table 1.

The search terms and strategies appear in Table 2.

V. Summary of Evidence

A. Summary of Findings and Included Studies

The PubMed search yielded 13 hits, of which only one was relevant. The one relevant study obtained is an open-label nonrandomized trial (Gautret et al.) which was critically appraised (Appendix A).

An updated, differently-designed version of this initial study by Gautret et al. was appraised as well (Appendix B), bringing the total studies to two.

The French team of Gautret and co-authors enrolled patients above 12 years of age, who had PCR-documented SARS-CoV-2 carriage in the admission nasopharyngeal swab regardless of clinical presentation. The study enlisted an initial 42 patients from The Mediterranee Infection Hospital Institute in Marseille, trimmed down to 36 total after loss to follow-up. Twenty-six patients were enrolled in the experimental group but there were six lost to follow-up, leaving 20 in the final analysis (hydroxychloroquine 14 patients, hydroxychloroquine plus azithromycin, six patients). Hydroxychloroquine was given at a dose of 200 mg three times a day for ten days; azithromycin at 500 mg for Day 1, followed by 250 mg for four days. There were 16 patients in the control arm, taken from other French medical centers, and given "symptomatic treatment and antibiotics." The outcome to be measured was virologic clearance at Day 6 post-inclusion. The investigators reported that at the time of assessment, 100% of those given hydroxychloroquine and azithromycin were virologically cured, compared to 57.1% of those given hydroxychloroquine alone, and 12.5% in the control group, and this was statistically significant ($p<0.001$).

The later study by Gautret et al., which enrolled 80 patients, is a descriptive observational study (no comparison group). Unlike the earlier, smaller study, the latter one looked at the clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin given for at least three days in patients with at least a six-day follow-up period. The study declared as endpoints 1) clinical outcome, 2) contagiousness as measured by PCR and culture, and 3) length of stay in an infectious disease unit. This study included the six patients from the open-label trial who received the combination regimen.

The authors reported that patients with no contraindications were offered 200 mg of oral HCQ (three times a day for ten days) combined with azithromycin (500mg on the first day, then 250 mg for the following four days). Out of 80 patients, 79 were managed this way. The majority of patients (81.3%) had favorable outcome and were discharged from the unit "at the time of writing (not indicated)." Ninety-three percent (93%) of patients were negative for viral load on Day 8 of treatment, and none of the patients were considered contagious on Day 12. The average time from initiation of treatment to discharge was 4.1 days. Seven out of 80 patients had adverse events of nausea and vomiting, diarrhea and blurring of vision (reported five days after treatment).

The search for studies on clinicaltrials.gov revealed four clinical trials due to begin in April 2020. A summary of studies found is given on Table 3.

No studies on hydroxychloroquine and azithromycin together for the treatment of COVID-19 appeared in the search of the Chinese Clinical Trial Registry, PROSPERO, CENTRAL, ISRCTN.

B. Summary of Guidelines

A review of guidelines that appear on UpToDate included those of CDC, WHO, Canada, and University of Michigan.

According to the CDC, there is currently no specific treatment that is available for COVID-19. Clinical management is hinged on "prompt implementation of recommended infection prevention and control measures" as well as the supportive management of complications, that may include advanced organ support as indicated.

The guideline by the University of Michigan recommends against routine use of azithromycin. Authors cited the data from the initial study of Gautret et al. and they pointed out that when analysis of the study participants was limited to those whose baseline cycle threshold values were comparable, combination therapy with hydroxychloroquine and azithromycin led to a similar proportion of negative testing by day 6 compared to hydroxychloroquine monotherapy. It is true that the study did not report the clinical outcomes of these patients, and it failed to show if virologic cure correlated with clinical improvement. On this basis, the University of Michigan cites it as weak evidence and "recommends against the routine use of azithromycin for the treatment of COVID-19 at this time."

The Canadian guideline generally states that currently there is neither a vaccine against COVID-19 or a specific treatment it. According to them, "treatment is supportive and should be tailored to the patient's condition."

The WHO has also published guidance on the clinical management of severe acute respiratory infection when novel coronavirus infection is suspected, but does not specifically recommend hydroxychloroquine with azithromycin.

VI. Conclusions and Implications for Decision

The evidence of possible benefit from the combination of hydroxychloroquine and azithromycin comes from an open-label, non-randomized clinical trial and should be approached with a critical eye. This risk, along with the known toxicities of both medications, should be weighed against the potential benefit of eliminating viral load, decreasing infectivity, and improving clinical outcomes in patients who otherwise have no way of combating the pandemic. With the view that the combination regimen may save lives, hence relieving the healthcare system at least temporarily, the medication should be offered patients and decision-making shared between them and their healthcare professional. Critical monitoring of hospital course and expected adverse events is warranted. In the meantime, more studies of larger sample sizes are awaited for more definitive conclusions.

VII. Declaration of Conflict of Interests

The reviewer declares no conflict of interest in any form or manner.

Prepared by: Maria Teresa Tolosa, MD, Diploma in Clinical Epidemiology
March 30, 2020

Rapid Review: Lopinavir/ritonavir

Should lopinavir/ritonavir combination be used in the treatment of COVID-19?
This is a rapid review on available evidences regarding the use of lopinavir/ritonavir to COVID-19. This may change as new evidences emerges.

Background
Lopinavir/ritonavir (LPV/r) is a combination drug used primarily in HIV infections. Lopinavir is a protease inhibitor while ritonavir increases the concentration of lopinavir. Early case reports have shown that lopinavir/ritonavir may be beneficial in patients with COVID-19.[1-3]

Search of Literature
The following electronic databases were searched for evidences: Medline, CENTRAL, ISRCTN registry, ClinicalTrial.gov and Chinese Clinical Trial Registry. See Annex A.

Evidence
The LOTUS trial is an open-label randomized controlled clinical trial involving 199 patients with laboratory confirmed SARS-COV-2 infection. The treatment group was given lopinavir-ritonavir plus standard of care while the control group was given standard of care alone. Standard of care comprised as necessary, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO). Time to clinical improvement was measured using a seven-category ordinal scale or live discharge from the hospital whichever came first. In both the intention to treat and the modified intention to treat analysis, lopinavir/ritonavir has no to little benefit in clinical improvement [intention to treat HR = 1.31 (95%CI: 0.95 to 1.85), modified intention to treat HR = 1.39 (95%CI: 1.0 to 1.91)]. Lopinavir-ritonavir group had a shorter stay in the intensive care unit (ICU) by as much as 9 days but as little as less than one day. The 28-day mortality is was lower in the lopinavir-ritonavir group but was not statistically significant. There were more serious adverse events such as acute kidney injury and acute respiratory failure in the standard group compared to the lopinavir-ritonavir group. Viral load was higher among those in the lopinavir/ritonavir group.[4]

There are at least 16 clinical trials on lopinavir-ritonavir including a WHO-initiated worldwide clinical trial. See Table 1.

Table 1.Ongoing clinical trials for lopinavir-ritonavir

Clinical Trial Identifier (Location)	Official Title	Methodology	Groups	Estimated Date of Completion
ISRCTN83971151 (Multicountry)	Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	Open-label randomized multicountry clinical trial	1. Local standard of care alone OR local standard of care plus one of 2. Remdesivir 3. Chloroquine or hydroxychloroquine 4. Lopinavir + ritonavir 5. Lopinavir + ritonavir plus interferon-beta	March 2021
NCT04307693 (South Korea)	Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	Multicenter open labelled, parallel randomized clinical trial	Experimental: Lopinavir/ritonavir Active Control: Hydroxychloroquine Control: No intervention	May 2020

NCT04261907	Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	Multicenter open labelled, parallel randomized clinical trial	Experimental: ASC09/ritonavir group + conventional standardized treatment Control: Lopinavir/ritonavir tablet+conventional standardized treatment	June 30,2020
NCT04252885 (China)	The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI)	Randomized open labelled, parallel clinical trial	Experimental: Lopinavir/ritonavir + standard treatment Active Control: Arbidol + standard treatment Control: Standard treatment alone	July 31, 2020
NCT04276688 (Hong Kong)	Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	Randomized, open label parallel controlled clinical trial	Experimental: Lopinavir/ritonavir + ribavirin + Interferon Beta-1B Active Control: Lopinavir+ritonavir	July 31,2022
NCT04255017 (China)	A Prospective/Retrospective , Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	Randomized single-blinded parallel controlled clinical trial	Experimental: Abidol HCl + standard treatment Experimental: Oseltamivir + standard treatment Experimental: Lopinavir/ritonavir + standard treatment Control: Standard treatment alone	July 1, 2020
NCT04315948 (France)	Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)	Randomized multi-center, open label, parallel controlled clinical trial	Experimental: Remdesivir Experimental: Lopinavir/ritonavir Experimental: Lopinavir/ritonavir plus Interferon B-1a Experimental: Hydroxychlorquine	March 2023
NCT04303299 (Thailand)	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19 : A Randomized Control Trial	Randomized multi-center, open label, parallel controlled clinical trial	Experimental groups: Various combinations of protease inhibitors, oseltamivir, favipriavir, and chlroquine	November 30, 2020

ChiCTR2000030187 (China)	Clinical study for Lopinavir and Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19)	Randomized controlled clinical trial	Experimental group: Lopinavir/ritonavir Control: Routine symptomatic support treatment	March 25 2020
ChiCTR2000029741 (China)	Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study	Randomized multi-center, open label, parallel controlled clinical trial	Experimental group: Chloroquine Control: Lopinavir/ritonavir	December 2020
ChiCTR2000029548 (China)	Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	Randomized open label, parallel controlled clinical trial	Experimental groups: 1. Baloxavir Marboxil 2. Favipiravir 3. Lopinavir-Ritonavir	June 2020
ChiCTR2000029541 (China)	A randomised, open, controlled trial for darunavir/cobicistat or Lopinavir/ritonavir combined with thymosin a1 in the treatment of novel coronavirus pneumonia (COVID-19)	Randomized open label, parallel controlled clinical trial	Experimental groups: 1. Darunavir/cobicistant + thymosin 2. Lopinavir/ritonavir + thymosin 3. Conventional treatment + thymosin	December 2020
ChiCTR2000029539 (China)	A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild novel coronavirus pneumonia (COVID-19)	Randomized open label, parallel controlled clinical trial	Experimental : Lopinavir ritonavir + conventional treatment Control: conventional treatment	February 2021
ChiCTR2000029468 (China)	A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of novel coronavirus pneumonia (COVID-19)	Non-randomized controlled clinical trial	Experimental : Lopinavir/litonavir (LPV/r)+ emtritabine (FTC)/ Tenofovir alafenamide Fumarate tablets (TAF) in combination Historical Control: Lopinavir/Ritonavir	June 2020
ChiCTR2000029387	Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alphain in patients with mild to moderate novel coronavirus pneumonia	Randomized controlled clinical trial	Experimental groups: 1. Ribavirin + Interferon alpha-1b 2. lopinavir / ritonavir + interferon alpha-1b 3. Ribavirin + LPV/r+Interferon alpha-1b	January 2021

ChiCTR2000029308	A randomized, controlled open-label trial to evaluate the efficacy and safety of lopinavir-ritonavir in hospitalized patients with novel coronavirus pneumonia (COVID-19)	Randomized open label, parallel controlled clinical trial	Experimental group: Lopinavir ritonavir Control group: Conventional treatment	January 2021

Conclusion

Based on one clinical trial, there is no to little benefit in clinical improvement among patients with severe COVID-19 if given early. However, more studies are needed to confirm whether the risk for complications such as respiratory failure and ARDS can be reduced by administration of lopinavir-ritonavir .

At this time, there is insufficient evidence to conclude on the effectiveness of lopinavir/ritonavir in patients with COVID-19. More high-quality randomized controlled trials are needed.

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Prepared by: Ian Theodore Cabaluna, MD, Diploma in Clinical Epidemiology

March 27, 2020

Rapid Review: Remdesivir

Should remdesivir be used in the treatment of COVID-19?
This is a rapid review on available evidences regarding the use of remdesivir to COVID-19. This may change as new evidences emerges.

Background
Remdesivir (GS-5734) is an investigational drug developed for the Ebola virus and is currently, being tested for the treatment of COVID-19. It is a nucleotide analogue that inhibits RNA-dependent RNA polymerases[1]. Several in-vitro studies in cells, primates and mouse demonstrated its antiviral activities against an array of RNA viruses (e.g. MERS-COV, Ebola Virus, SARS-COV)[2-4].

Literature Search
A comprehensive search of two electronic databases (Medline, CENTRAL) were done. The following clinical trial registry were also searched: ISRCTN registry, ClinicalTrial.gov and Chinese Clinical Trial Registry. See Annex A.

Evidence
There is limited published clinical studies on remdesivir. An in-vitro study on infected Vero cells have shown that remdesivr can reduce the amount of COVID-19 virus[5]. Currently there are at least 8 ongoing clinical trials on remdesivir. This include the WHO-initiated study, the Solidarity Trial, that would involve testing remdesivir, chloroquine, lopinavir+ritonavir and interferon-beta.

Table 2.Ongoing clinical trials for remdesivir

Clinical Trial Identifier (Location)	Official Title	Methodology	Groups	Estimated Date of Completion
ISRCTN83971151 (Multicountry)	Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	Open-label randomized multicountry clinical trial	1. Local standard of care alone OR local standard of care plus one of 2. Remdesivir 3. Chloroquine or hydroxychloroquine 4. Lopinavir + ritonavir 5. Lopinavir + ritonavir plus interferon-beta	March 2021
NCT04257656 (China)	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoVRespiratory Disease.	Randomized multicenter double blind controlled trial	Experimental: Remdesivir Control Remdesivir Placebo	May 1, 2020
NCT04252664 (China)	A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult	Randomized multicenter double blind controlled trial	Experimental: Remdesivir Control Remdesivir Placebo	April 27,2020

	Patients With Mild and Moderate 2019-nCoV Respiratory Disease.			
NCT04292899 (USA, Hong Kong, Spain, Taiwan, Singapore and Korea)	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	Randomized multicenter open label controlled trial	Experimental: Remdesivir Control: Standard of Care	May 2020
NCT04292730 (USA, Hong Kong, Spain, Taiwan, Singapore and Korea)	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment	Randomized multicenter open label controlled trial	Experimental: Remdesivir Control: Standard of Care	May 2020
NCT04280705 (USA, Japan, Korea, Singapore)	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	Randomized multicenter double blinded controlled trial	Experimental: Remdesivir Control: Placebo	April 1, 2023
NCT04321616 (Norway)	The (Norwegian) NOR Solidarity Multicenter Trial on the Efficacy of Different Anti-viral Drugs in SARS-CoV-2 Infected Patients	Open labelled randomized adaptive controlled trial	Experimental: 1. Remdesivir 2. Hydroxychloroquine 3. Standard of care	November 2020
NCT04315948 (France)	Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)	Multi-centre, adaptive, randomized, open clinical trial	Experimental: 1. Remdesivir 2. Lopinavir/ritonavir 3. Interferon Beta-1ADrug: 4. Hydroxychloroquine 5. Standard of care	March 2023

Recommendation from other international bodies

WHO interim guidance does not recommend any specific anti-viral or biologic but recommends symptomatic treatment for patients with COVID-19.[6]

Conclusion

There is insufficient evidence regarding the effectiveness of remdesivir in the treatment of COVID-19. Numerous clinical trials are still underway.

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Prepared by: Ian Theodore Cabaluna, MD, Diploma in Clinical Epidemiology

March 27, 2020

Rapid Review: Tocilizumab
Should tocilizumab be used in the treatment of COVID-19?

Background

Tocilizumab (Actemra/RoActemra) is an immunosuppressive drug used for treating various forms of arthritis. As a monoclonal antibody that binds to interleukin-6 (IL-6), it inhibits IL-6 signaling which consequently reduces inflammation. Its safety has been demonstrated in several studies (1-2).

Systemic hyperinflammation has been proposed as a key characteristic of the disease in patients with severe COVID-19 (3). Recent observational studies have shown significantly higher IL-6 levels and other inflammatory cytokines among non-survivors (4-5). Intravenous administration of tocilizumab is currently being used as one of the experimental treatments for patients with COVID-19; however, its efficacy and safety still needs to be investigated. In this rapid review, we summarize all available evidence regarding the efficacy and safety of tocilizumab for treating COVID-19.

Literature Search

A comprehensive search of two electronic databases (CENTRAL, Medline) and three clinical trial registries (ClinicalTrials.gov, Chinese Clinical Trial Registry (ChiCTR), EU Clinical Trials Register) was conducted. ChinaXiv.org was also searched for any relevant studies awaiting peer-review. (See Table 1)

Evidence

There are still no completed randomized clinical trials on this intervention. However, we found 1 unpublished case series (Xu et al., 2020) from China as well as 7 ongoing clinical trials.

The non-randomized case series by Xu et al. evaluated the efficacy of tocilizumab in treating 21 adult patients with severe or critical COVID-19. A case was diagnosed as severe if (1) respiratory rate > 30 breaths/min, (2) SpO2 < 93% while breathing room air, or (3) PaO2/FiO2 < 300 mmHg. Critical cases were defined if any of the conditions were present: (1) respiratory failure requiring mechanical ventilation, (2) shock, (3) combined with other organ failure, (4) requiring ICU admission. All patients have been on standard care (i.e. lopinavir, methylprednisolone, oxygen therapy, other symptom relievers) for at least 1 week with deteriorating symptoms before tocilizumab 400mg (intravenous drip) was added to their treatment regimen.

In this study, all 21 demonstrated normalization of body temperature on the first day after receiving tocilizumab. After 5 days, lymphocyte counts in 10/19 patients (52%) and CRP levels in 17/18 patients (94.4%) returned to normal. Improvements in lung CT scans and pulmonary function were also noted in 19 patients. No adverse events were reported, and 19/21 patients were eventually discharged (2 were still hospitalized when study was written). Average time of hospitalization after tocilizumab dose was 13.5 days. While the study authors concluded that tocilizumab is an effective treatment for severe COVID-19 cases, the study appears to be prone to methodological biases. The study design was observational and non-randomized, unblinded, and had incomplete outcome data (e.g. unclear dose and duration of methylprednisolone, IL-6 levels not documented).

Table 2 summarizes the characteristics of the 7 ongoing clinical trials on tocilizumab. Four studies are already recruiting participants (3 in China, 1 in Italy), while the rest are set to begin within the next 2 weeks. Most studies aim to investigate the effect of tocilizumab (8mg/kg) compared to placebo or standard medical care. Primary outcomes included were mortality or clinical status within 1 month, improvements in pulmonary function, and cure rate. Results from some studies are expected on May 2020. A study in China (NCT04310228) aims to compare efficacy of favipiravir combined with tocilizumab versus either favipiravir or tocilizumab only. A large, multi-center, double-blind, RCT (NCT04320615) targeting 330 adult patients is set to start recruitment on April 2020.

Recommendations from international or foreign institutions

WHO interim guidance does not recommend any specific antiviral or biologic at this time but emphasizes symptomatic treatment in patients with COVID-19 (WHO, 2020). On the other hand, the China National Health Commission recommends trying tocilizumab in cases of extensive lung lesions and severe patients with elevated IL-6. They do not recommend the use in people with active infections such as tuberculosis.(China National Health Commission)

Conclusion

Based on one observational study, there appears to be some benefit associated with the use of tocilizumab among patients with severe COVID-19. More clinical trials are needed to assess its efficacy and safety among COVID-19 patients with varying disease severity.

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Table 2. Characteristics of clinical trials studying the efficacy and safety of tocilizumab for patients with COVID-19

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Primary outcomes
1	ChiCTR2000029765 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)	Recruiting	02/10/20 – 05/10/20	Multi-center, double arm	China	Adults (18-85 yo) w/ severe COVID-19 pneumonia (n = 94)	Tocilizumab (unspecified dose) + conventional therapy	Conventional therapy	Cure rate (unspecified)
2	NCT04317092 / EudraCT 2020-001110-38 Multicenter Study on the Efficacy and Tolerability of Tocilizumab in the Treatment of Patients With COVID-19 Pneumonia	Recruiting	03/19/20 – 12/19/20	Multi-center, single arm, open-label, phase 2	Italy	Child, adult w/ severe COVID-19 pneumonia (n = 330)	Tocilizumab (RoActemra) 8 mg/kg (up to a maximum of 800mg per dose) BID	None	1-month mortality
3	NCT04310228 / ChiCTR2000030894 Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019-A Multicenter, Randomized and Controlled Clinical Trial Study	Recruiting	03/08/20 – 05/20	Multi-center RCT, open-label	China	Adult > 18 w/ COVID-19 (n = 150)	Favipiravir with tocilizumab - Favipiravir (1600mg BID day 1; 600mg BID day 2-7), oral - Tocilizumab (4 ~ 8mg/kg (up to a maximum of 800mg per dose)), IV	Favipiravir group (1600mg BID day 1; 600mg BID day 2-7), oral Tocilizumab group (4 ~ 8mg/kg (up to a maximum of 800mg per dose)), IV	Clinical cure rate in 3 months (i.e. viral load negative for 2 consecutive nucleic acid tests, improvement in lung image, normal body temperature for > 3 days, improved clinical manifestation)
4	NCT04306705 A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19	Recruiting	02/20/20 – 05/30/20	Retrospective cohort	China	Adults (18-80 yo) w/ COVID-19 (n = 120)	Tocilizumab 8mg/kg OD, IV	None	Proportion of participants with improved clinical status sustained for 72 hrs (fever normalization (< 36.6°C armpit or < 37.2°C oral; AND oxygen normalization (SpO2 > 94%))
5	NCT04320615 A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety	Not yet recruiting	04/03/20 – 08/31/21	Multi-center RCT, double-blind, phase 3	Multi-country	Adults > 18 w/ severe COVID-19 pneumonia (n = 330)	Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose), + 1 additional	Placebo (1 IV infusion of placebo matched to TCZ) + standard of care	Clinical status at day 28 assessed using a 7-category ordinal scale

	and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia						dose if clinical symptoms worsen or show no improvement, IV		
6	NCT04315480 Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 Infection With Severe Multifocal Interstitial Pneumonia	Not yet recruiting	03/20 – 04/20	Single center, single arm, open label, phase 2	Italy	Adults (18 – 80 yo) w/ severe COVID-19 pneumonia (n = 30)	Tocilizumab 8mg/kg, IV	None	Pulmonary function (rate of patients with stable pulmonary function OR with >+3% change of O2 saturation OR -10% in FiO2 need OR >30% reduction in pulmonary consolidations on HR CT-scan)
7	NCT04322773 Effectiveness of Interleukin-6 Receptor Inhibitors in the Management of Patients With Severe SARS-CoV-2 Pneumonia: An Open-Label, Multicenter Sequential and Cluster Randomized Trial	Not yet recruiting	03/25/20 – 06/01/21	Multicenter cluster RCT, sequential, open-label, phase 2	Denmark	Adults (>18 yo) w/ COVID-19 pneumonia (n = 200)	Tocilizumab (RoActemra) 400mg, IV OR Tocilizumab, 2 x 162mg, subcutaneous OR Sarilumab (Kevzara), 1 x 200mg, subcutaneous	Standard medical care	Time to independence from supplementary oxygen therapy (up to 30 days)

Prepared by: Howell Bayona, Diploma in Clinical Epidemiology
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