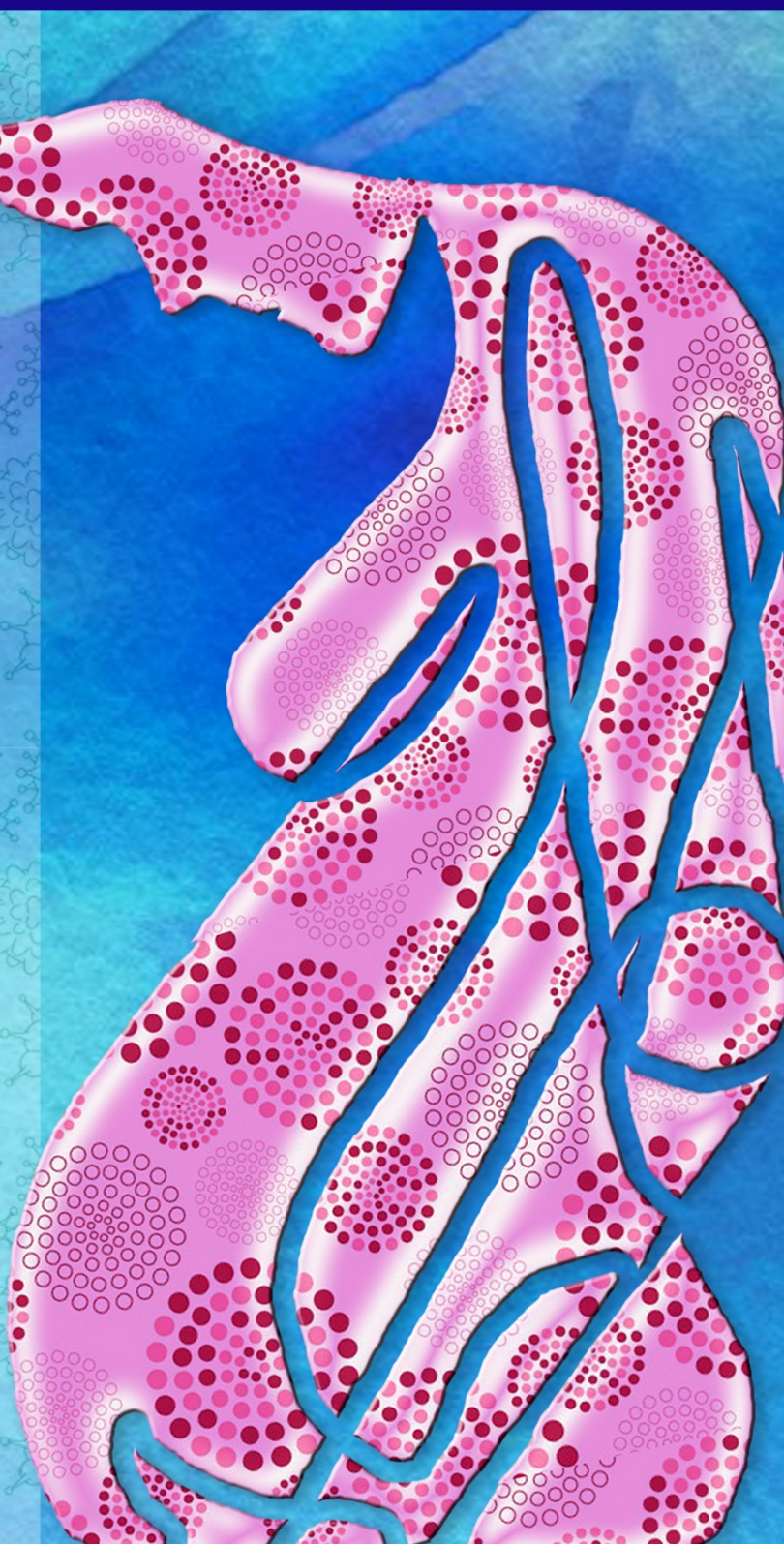
PHILIPPINE OBSTETRICAL AND GYNECOLOGICAL SOCIETY (Foundation), INC.

PHILIPPINE INFECTIOUS DISEASES SOCIETY
FOR OBSTETRICS AND GYNECOLOGY, INC.

The PIDSOG Handbook:

A GUIDANCE FOR CLINICIANS ON THE OBSTETRIC MANAGEMENT OF PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID-19)



OCTOBER 2020
SECOND EDITION

PIDSOG HANDBOOK: A GUIDANCE FOR CLINICIANS ON THE OBSTETRIC MANAGEMENT OF PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID-19)

Second Edition

Philippine Obstetrical and Gynecological Society (Foundation), Inc.

Philippine Infectious Diseases Society for Obstetrics and Gynecology, Inc.

MESSAGE FROM THE POGS PRESIDENT

PHILIPPINE OBSTETRICAL AND GYNECOLOGICAL SOCIETY (Foundation), INC.

The Philippine Obstetrical and Gynecological Society (Foundation), Inc. would like to congratulate the Philippine Infectious Diseases Society for Obstetrics and Gynecology Inc. (PIDSOG) for coming out with the handbook on 'A Guidance for Clinicians on the Obstetric Management of Patients with COVID-19 Infection (An Update).'

At the outset of the COVID-19 pandemic in March, PIDSOG together with POGS worked on providing guidance to the general membership to ensure that there is a continuity of care to our patients. This handbook showcases the cohesiveness and the dedication of the membership of PIDSOG with the objective of providing the right way to handling COVID -19 patients during these very challenging times.

More importantly, this handbook is not for the exclusive use of POGS but rather meant to be shared with the generalists, family physicians and other specialties. I am proud that during my presidency, PIDSOG was able to rise up to the occasion in providing this handbook.

CHRISTIA S. PADOLINA, MD, FPOGS, FPSUOG
President
Philippine Obstetrical and Gynecological Society (Foundation), Inc

MESSAGE FROM THE PIDSOG PRESIDENT

PHILIPPINE INFECTIOUS DISEASES SOCIETY FOR OBSTETRICS AND GYNECOLOGY SOCIETY, INC.

I salute the officers and members of the Philippine Infectious Diseases Society for Obstetrics and Gynecology, Inc. (PIDSOG) for coming up with timely and relevant recommendations during this COVID-19 pandemic. Truly, an act of commitment and devotion that you have shown to our profession and to our beloved society.

The limited information and experience on COVID-19 paved the way for the immediate development of this handbook entitled, *A Guidance for Clinicians on the Obstetric Management of Patients with Coronavirus Disease 2019*. This handbook will provide a better understanding of the diagnosis, management, treatment and prevention of COVID-19 infection in the pregnant population.

On behalf of the PIDSOG 2019-2020 Board of Directors, my sincerest appreciation to the members of the technical working group for their relentless efforts and dedication in the completion of this handbook amidst these challenging times. Likewise, I extend my deepest gratitude to the different stakeholders who have contributed and supported the cause for which this handbook was formulated.

Lastly, we share the PIDSOG Handbook to all our colleagues and other allied professions involved in the care of the pregnant woman. I hope this handbook will be of great help as we continue our fight and show resilience with our elusive opponent. Always remember to keep safe and God bless everyone.

ERWIN R. DE MESA, MD, FPOGS, FPIDSOG
President
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FOREWORD

Early this year, the world was shaken by a novel virus, SARS-CoV-2, which has led to the COVID-19 disease pandemic. While we continue to tread through the uncertainties brought by this emerging infection, we aim to maintain provision of appropriate and optimal care to our pregnant patients under the “new normal.”

This handbook was created with the intention to provide guidance to our fellow colleagues – obstetricians in practice, residents and fellows in training, midwives, primary care physicians and other allied medical practitioners – in managing COVID-19 in pregnant patients.

Current data and information on SARS-CoV-2 and COVID-19 is dynamic. Hence, some information in this handbook may be subject to change over time. Rest assured that our team will tirelessly update this guide as new and stronger evidence is discovered in the future.

In the age of globalization, this pandemic has changed the facet of our daily living, more so, the practice of medicine. The way to win this war is through sharing of knowledge, information, resources and experience. It is in our sincerest hope that this handbook will provide its readers with the armamentarium to fight and succeed over the invisible and formidable adversary.

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SUMMARY OF UPDATES

EDITION	DATE OF RELEASE	UPDATES
2nd	October 2020	**DIAGNOSIS OF COVID-19 IN PREGNANCY** ▪ What are the types of tests available for COVID-19? – ***NEW*** ▪ Can antigen test be used in the diagnosis of COVID-19 infection? – ***NEW*** ▪ Is there a role for antibody (serology) testing in diagnosing COVID-19? – ***NEW*** ▪ Is repeat testing warranted at term or prior to delivery in pregnant patients who tested positive for COVID-19 remote from delivery? – ***NEW***
2nd	October 2020	**MANAGEMENT OF COVID-19 IN PREGNANCY** ▪ Are pregnant patients at higher risk for getting COVID-19? – ***Updated*** ▪ What are the known obstetric complications of COVID-19 infection? – ***Updated*** ▪ Can COVID-19 infect the fetus in-utero? – ***Updated*** ▪ Should corticosteroids be given to pregnant women in preterm labor with COVID-19 infection? – ***Updated*** ▪ Can mothers with COVID-19 infection breastfeed their infants? – ***Updated*** ▪ What are the criteria for discharging COVID-19 pregnant patients and when should they be scheduled for follow-up? – ***NEW***
2nd	October 2020	**INVESTIGATIONAL DRUGS USED FOR COVID-19** ▪ What are the treatment options for pregnant and lactating women infected with COVID-19? – Efficacy of Remdesivir in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Tocilizumab in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Corticosteroids in the treatment of COVID-19 infection – ***Updated*** – Safety issues on the use of Corticosteroids – ***Updated*** – Dosage of Corticosteroids in the treatment of COVID-19 – ***Updated*** – Efficacy of Immunoglobulin in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Melatonin in the treatment of COVID-19 infection – ***Updated***

		– Efficacy of Zinc in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Ascorbic Acid in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Oseltamivir in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Lopinavir/Ritonavir in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Favipiravir in the treatment of COVID-19 infection – ***Updated*** – Efficacy of Azithromycin in the treatment of COVID-19 infection – ***Updated*** – Chloroquine and Hydroxychloroquine – ***Updated*** – Convalescent Plasma – ***NEW*** – Plasmapheresis and Therapeutic Plasma Exchange – ***NEW*** ▪ What are the vaccines being developed against SARS-CoV-2? – ***NEW***

BACKGROUND ON COVID-19

Sybil Lizanne R. Bravo, RPh, MD, MSc

WHAT IS A PANDEMIC?

Pandemic is defined as *"an outbreak of a disease that occurs over a wide geographical area and affects an exceptionally high proportion of the population,*[1]*"* or as defined by the World Health Organization (WHO), *"is the worldwide spread of a new disease.*[2]*"*

The world has suffered a number of pandemics. There was the 1918 Spanish flu wherein millions died. About eighteen years ago, we had the 2002-2004 severe acute respiratory syndrome (SARS), which was also caused by a coronavirus. And of course, there is the Ebola contagion which has originated in the African region but made its way to some countries and which has baffled scientists all over.

Who would have thought that, indeed, in our lifetime, we would experience a pandemic? This current COVID-19 pandemic has indeed been a conundrum for men of science.

COVID-19 AND SARS-CoV-2

As detailed by the World Health Organization (WHO), there are two official names for this pathogen – COVID-19 refers to the coronavirus disease, while severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is used when referring to the virus itself.[3]

Last February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) announced the term SARS-CoV-2, because this current virus is genetically related to the coronavirus that caused the SARS outbreak in year 2003.

CLINICAL PRESENTATION OF COVID-19?

As of current knowledge and with global experience, a substantial proportion of severely ill patients may require intensive care. The main reason for admission into an intensive care unit is mainly due to viral pneumonitis that evolves into acute respiratory distress syndrome (ARDS). The usual symptoms are fever, cough, sore throat, and malaise. The onset of difficulty of breathing is on day 5 to day 7, though progression into ARDS may be fast thereafter, about 2-3 days from difficulty of breathing. Almost half to all who are critically ill would eventually require mechanical

ventilation. Complications include acute renal failure, liver enzyme elevation, cardiac pathologies such as cardiomyopathy, arrhythmia and sudden cardiac death, septic shock, secondary bacterial pneumonia, altered lung compliance, and encephalopathy. In lieu of these complications, it is imperative that healthcare providers offer what they think and believe are best supportive forms of management including the use of some investigational pharmacological therapies.

In these past few months, risk factors have been identified and most healthcare providers agreed that there are at-risk or vulnerable populations, such as the elderly, the young, and those with immunocompromising conditions. Pregnant women, in any disease state, are considered a vulnerable population.

As such, this handbook will function as guidance for obstetrician-gynecologists and other healthcare providers who tirelessly devote much of their time and effort in making sure our Filipino gravidas and their unborn children will be given, if not the definitive, but as of current situation, the most ideal and applicable management.

While it is true that knowledge of the pathophysiology, the virulence of this contagion, and the therapy of this infection are very much in evolution, the authors of this guidance hope that this will be of assistance to everyone involved in the care of our pregnant women as the following are discussed: diagnosis, management, treatment and prevention including proper use of personal protective equipment.

It is with great honor and dedication that we have revised the PIDSOG Handbook on Guidance for Clinicians on the Obstetric Management of Patients with COVID-19. It is timely that this handbook was reviewed and edited because of updated research on the diagnosis and management of this infection especially as we deal with pregnant women. This edited version discusses the latest updated evidence on diagnosis. More importantly, this newer version discusses the up to date pharmacologic therapy. With thirst for knowledge and search for the appropriate drugs to treat our women, we present in this latest guidance evidence for or against the uses of some of the drugs mentioned in the original version. We hope to have imparted as much updated and consistent literature there is available at current time in this guidance.

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DIAGNOSIS OF COVID-19 IN PREGNANCY

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WHAT ARE THE CASE DEFINITIONS FOR COVID-19 IN PREGNANT WOMEN?

STATEMENT:

The case definitions for COVID-19 in pregnant women are no different from that of the general population. The terms SUSPECTED case, PROBABLE case and CONFIRMED case are used.

SUPPORTING STATEMENTS:

Suspected case

A patient with acute respiratory tract infection (i.e. sudden onset of at least one of the following: fever, cough, shortness of breath) AND with no other etiology that fully explains the clinical presentation AND with a history of travel or residence in a country/area reporting local or community transmission during the 14 days prior to symptom onset;

OR
A patient with any acute respiratory illness AND having been in close contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms;

OR
A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable Case

A suspected case for whom testing for virus causing COVID-19 is inconclusive (according to the test results reported by the laboratory) or for whom testing was positive on a pan-coronavirus assay.

Confirmed Case

A person with laboratory confirmation of virus causing COVID-19 infection, irrespective of clinical signs and symptoms.

Close Contact

A close contact of a probable or confirmed case is defined as:

- A person living in the same household as a COVID-19 case;
- A person having had direct physical contact with a COVID-19 case (e.g. shaking hands);
- A person having unprotected direct contact with infectious secretions of a COVID-19 case (e.g. being coughed on, touching used paper tissues with a bare hand);
- A person having had face-to-face contact with a COVID-19 case within 2 meters and > 15 minutes;
- A person who was in a closed environment (e.g. classroom, meeting room, hospital waiting room, etc.) with a COVID-19 case for 15 minutes or more and at a distance of less than 2 meters;
- A healthcare worker (HCW) or other person providing direct care for a COVID-19 case, or laboratory workers handling specimens from a COVID-19 case without recommended personal protective equipment (PPE) or with a possible breach of PPE;
- A contact in an aircraft sitting within two seats (in any direction) of the COVID-19 case, travel companions or persons providing care, and crew members serving in the section of the aircraft where the index case was seated (if severity of symptoms or movement of the case indicate more extensive exposure, passengers seated in the entire section or all passengers on the aircraft may be considered close contacts).

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WHEN DO YOU SUSPECT THAT A PREGNANT PATIENT HAS COVID-19?

STATEMENT:

The possibility of COVID-19 infection is suspected in a pregnant woman with new-onset fever and/or respiratory symptoms. It should also be considered in a pregnant woman with severe lower respiratory tract illness without any clear cause.

SUPPORTING STATEMENTS:

Clinical findings

The clinical characteristics reported among pregnant women with confirmed COVID-19 infection are similar to those reported in non-pregnant adults in the general population. There are no specific clinical features that can reliably distinguish COVID-19 infection from other viral respiratory infections.

Pneumonia appears to be the most frequent serious manifestation of the infection, characterized by fever, cough, dyspnea, and bilateral infiltrates on chest imaging.[1-4] In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of illness were fever, cough, and dyspnea.[4]

Similarly, other cohort studies of patients from Wuhan with confirmed COVID-19 infection have reported a similar range of clinical findings.[2,3]

Table 2.1 COVID-19 Common Clinical Features

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

*NR – not reported

Nonetheless, the symptoms expressed by COVID-19 patients are nonspecific and cannot be used for an accurate diagnosis.

Other less common symptoms include headache, sore throat, and rhinorrhea. In addition to respiratory symptoms, gastrointestinal symptoms (e.g. nausea and diarrhea) have also been reported; and in some patients, these may be the presenting complaint.[2,4]

Reports of cohorts in locations outside of Wuhan have described similar clinical findings, although some have suggested that milder illness may be more common.[5-7] As an example, in a study of 62 patients with COVID-19 infection in the Zhejiang province of China, all but one had pneumonia, but only two developed dyspnea, and only one warranted mechanical ventilation.[6]

Anosmia has been anecdotally reported as a distinguishing symptom in patients who were ultimately diagnosed with COVID-19.[8] However, published cohort studies have not highlighted this symptom, and its frequency and utility in suspecting COVID-19 infection is uncertain.

Laboratory findings

In patients with COVID-19 infection, the white blood cell count can vary. Leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common.[9] Elevated lactate dehydrogenase and ferritin levels are common, and elevated aminotransferase levels have also been described. On admission, many patients with pneumonia have normal serum procalcitonin levels. However, in those requiring ICU care, they are more likely to be elevated.[2-4] High D-dimer levels and more severe lymphopenia have been associated with mortality.[3]

Inflammatory Markers

Serum Procalcitonin

Serum procalcitonin is often normal on admission, however, it increases in patients who require ICU care.

C-reactive protein (CRP)

COVID-19 infection increases CRP. This seems to track with disease severity and prognosis. In patients suffering from with severe respiratory failure with a normal CRP level an alternative diagnosis should always be sought.[10]

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WHO SHOULD BE TESTED FOR COVID-19?

STATEMENT:

All pregnant women with symptoms associated to COVID-19 infection should be tested. Testing should also be considered in pregnant women with increased of exposure to the diseases, such as those who reside in or has a history of travel within the prior 14 days to a location with community transmission or those who had close contact with a confirmed or suspected case of COVID-19.

SUPPORTING STATEMENTS:

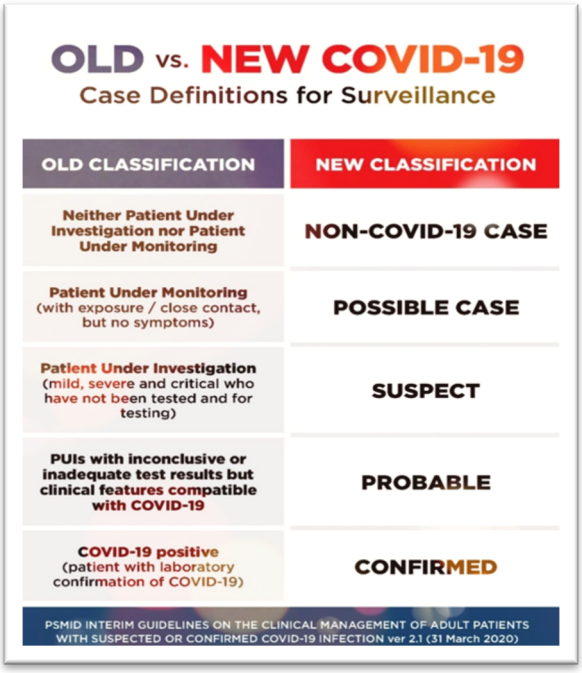

Figure 2.1 Case Definition Classification

Testing is done based on approved local protocols. Current guidelines do not recommend testing for asymptomatic individuals with no comorbidities.[1]

Although the DOH has recognized the pregnant population as a "vulnerable" group, the evidence, so far, have shown that pregnant women are still no more likely to contract the infection than the general population. In fact, the Infectious Disease Society of America (IDSA) classified pregnant women under "Tier 3" for COVID-19 Prioritization Testing.[2] However, pregnancy in a small proportion of women, may alter the response of the body to severe viral infections, and as such, some pregnant women may be at a greater risk for severe illness, morbidity or mortality compared with the general population.

Hence, pregnancy alone in the setting of new-flu like symptoms is sufficient to warrant COVID-19 testing, especially if additional risk factors (e.g. close contact with a known COVID-19 case, immunocompromised, with comorbidities such as hypertension, diabetes, etc.) are identified in the patient.

The possibility of COVID-19 should be considered primarily in patients with new onset fever and/or respiratory tract symptoms. It should also be considered in patients with severe lower respiratory tract illness without any clear cause.

Although these syndromes can occur with other viral respiratory illnesses, the likelihood of COVID-19 is increased if the patient:

- Resides in or has traveled within the prior 14 days to a location where there is community transmission of COVID-19 (i.e. large numbers of cases that cannot be linked to specific transmission chains) OR
- Has had close contact with a confirmed or suspected case of COVID-19 in the prior 14 days, including those who work in health care settings.

Close contact includes being within approximately six feet (about two meters) of a patient for a prolonged period of time while not wearing personal protective equipment or having direct contact with infectious secretions while not wearing personal protective equipment.

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SHOULD ASYMPTOMATIC PREGNANT WOMEN BE SCREENED FOR SARS-CoV-2 PRIOR TO DELIVERY?

STATEMENT:

Asymptomatic individuals play a role in the transmission of COVID-19. Hence, screening for SARS-CoV-2 should be considered among pregnant women at 37 – 38 weeks to give time for the release of the results prior to delivery or as close to the day of delivery whenever possible.

SUPPORTING STATEMENTS:

Experience with COVID-19 in pregnancy is limited. To date, data is based on case-series that are not controlled. The background comorbidities in the population, local testing policies, and obstetric care practices may limit generalizability to our population.

Identifying pregnant women with COVID-19 infection has several goals:

1. To tailor frequency and location of prenatal care for identified COVID-19 confirmed women and COVID suspects and probable cases.
2. To decrease risk of transmission to other patients, healthcare personnel, and family living in the same space
3. To plan for labor and delivery care
4. To plan for mother-infant separation strategies, if necessary

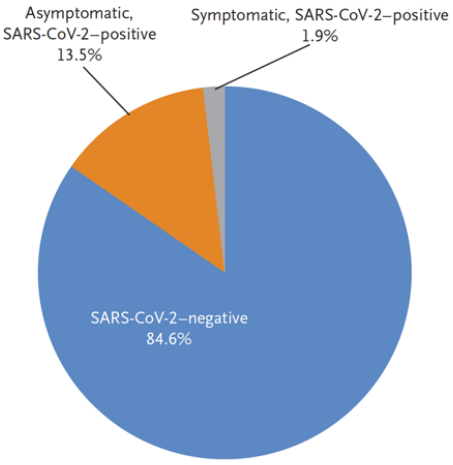

Figure 2.2 Symptom status and SARS-CoV-2 test results among 215 obstetrical patients presenting for delivery. (SOURCE: Adapted from Sutton NEJM)

Rate of Asymptomatic Women with Positive SARS-CoV-2 Results

Pregnancy alone in the setting of new flu-like symptoms is sufficient to warrant COVID-19 testing especially if with additional risk factors (e.g. close contact with known COVID-19 case, immunocompromised, with co-morbidities e.g., hypertension, diabetes). However, patients may present early in their infectious course prior to symptoms or may have asymptomatic viral carriage.

In a series of 43 COVID-19 infected pregnant women in New York, 32.6% of them presented WITHOUT symptoms. Of these, 46.2% developed symptoms within 7 days after the positive test.[1]

A recent series (by Sutton et al.) of 215 pregnant patients from New York demonstrated a 13.7% rate of positive testing for SARS-CoV-2 amongst asymptomatic women (4/215 had fever, while 211/215 were asymptomatic). Nasopharyngeal swabs were obtained from 210 of the 211 women (99.5%) who did not have symptoms of COVID-19. Of these women, 29 (13.7%) were positive for SARS-CoV-2. Thus, 4 out of 33 patients who were positive for SARS-CoV-2 on admission were symptomatic (12.1%), while 29 of the 33 patients who were positive for SARS-CoV-2 at admission (87.9%) had no symptoms of COVID-19 at presentation.[2]

Sutton et al. said that "use of universal SARS-CoV-2 testing in all pregnant patients presenting for delivery revealed that at this point in the pandemic in New York City, most of the patients who were positive for SARS-CoV-2 at delivery were asymptomatic". **This highlights the risk of COVID-19 infection in asymptomatic pregnant women.** Hence, they concluded that the potential benefits of a universal testing approach include the ability to use COVID-19 status to determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of personal protective equipment.[2] This report in a high prevalence area demonstrated 1 out of 8 asymptomatic pregnant patients presenting for delivery were SARS-CoV-2 positive, illustrating a need for universal screening.

Another New York study was done by Vintzileos et al. with the primary objective of determining the accuracy of maternal symptomatology in predicting the COVID-19 infection as confirmed by rapid laboratory testing using GeneXpert SARS-CoV-2 Nasopharyngeal Sample Collection Kit.[3] A total of 161 patients underwent routine COVID-19 testing on admission to labor and delivery room. Of the 161 patients tested, 32 (19.9%) were COVID-19 positive and of these, 11 (34%) were symptomatic and 21 (66%) were asymptomatic.[3]

Table 2.2 Accuracy of maternal symptomatology in predicting the COVID-19 infection[3]

	Positive COVID-19	**Negative COVID-19**	**Total**
Symptomatic	11	5	16
Asymptomatic	21	124	145
Total	32	129	161

Note. Sensitivity = 11/32 (34.4%); specificity = 124/129 (96.1%); positive predictive value = 11/16 (68.7%); negative predictive value = 124/145 (85.5%); positive likelihood ratio = 8.8; negative likelihood ratio = 0.68.

Can these numbers be generalizable to areas with lower infection rates like the Philippines? It would be good to know how transmission rates differ between symptomatic carriers and those who are asymptomatic. As this pandemic evolves, we are learning more and more, and it is important to expand our understanding of asymptomatic transmission and the risk this may pose.

Key benefits to screening are the capability for labor and delivery units to implement best hospital practices in their care of mothers and babies, such as admitting confirmed patients to cohort units. Such units would allow for closer monitoring of mothers and babies, as well as ensuring proper use of personal protective equipment by health care teams and also would help preserve supplies of personal protective equipment.

Hospital testing capacity is an obvious barrier to screening of pregnant women, as well as factors like the need for additional protective equipment to be used during swab collection. Also, if you get a negative result and there is a strong suspicion for COVID-19 infection, when do you retest? These are key questions or areas of assessment that should be considered before embarking on screening for pregnant women. In addition, some patients may refuse testing out of fear of stigma or separation from their newborn.

Implementing an 'opt out' approach to screening may be encouraged, whereby a patient is informed that a test will be included in standard preventive screening, and they may decline the test. Routine, opt-out screening approaches have proven to be highly effective as it removes the stigma associated with testing, fosters earlier diagnosis and treatment, reduces risk of transmission, and has proven to be cost effective. Pregnant women should be reassured that screening is beneficial for their care and the care of their newborn baby.

Traditional infection control and public health strategies rely heavily on early detection of disease to contain spread. When COVID-19 burst onto the global scene, public health officials initially deployed interventions that were used to control severe acute respiratory syndrome (SARS) in 2003, including symptom-based case detection and subsequent testing to guide isolation and quarantine.

This initial approach was justified by the many similarities between SARS-CoV-1 and SARS-CoV-2, including high genetic relatedness, transmission primarily through respiratory droplets, and the frequency of lower respiratory symptoms with both infections developing a median of 5 days after exposure. However, despite the deployment of similar control interventions, the trajectories of the two epidemics have veered in dramatically different directions.

What explains these differences in transmission and spread? A key factor in the transmissibility of Covid-19 is the high level of SARS-CoV-2 shedding in the upper respiratory tract, even among pre-symptomatic patients, which distinguishes it from SARS-CoV-1, where replication occurs mainly in the lower respiratory tract.[4,5] Viral loads with SARS-CoV-1, which are associated with symptom onset, peak a median

of 5 days later than viral loads with SARS-CoV-2, which makes symptom-based detection of infection more effective in the case of SARS-CoV-1.[6]
Ultimately, the rapid spread of COVID-19 across the globe, the clear evidence of SARS-CoV-2 transmission from asymptomatic persons, and the eventual need to relax current social distancing practices argue for broadened SARS-CoV-2 testing to include asymptomatic persons even in low epidemics.

Depending on the availability of testing capacity and resources, institutions should consider implementing screening on labor and delivery as several geographic areas are predicted to reach their peak time of COVID-19 transmission, and it is clear that asymptomatic individuals continue to play a role in its transmission. It may be more prudent to conduct the testing at 37-38 weeks, giving a lead time for the release of results prior to delivery. If labor ensues >14 days from the last testing, repeat testing may be done, if resources would allow (Appendix A).

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WHAT ARE THE TYPES OF TESTS AVAILABLE FOR COVID-19?

STATEMENT:

There are two types of test for COVID-19 – diagnostic test and antibody test.

SUPPORTING STATEMENTS:

A **diagnostic test** detects the virus and can show if you have an active COVID-19 infection. These include **molecular** tests, such as RT-PCR tests, that detect the virus's genetic material, and **antigen** tests that detect specific proteins on the surface of the virus).

An **antibody test,** i.e., serological tests, looks for antibodies that are made by your immune system in response to the infection to help determine whether the individual being tested was previously infected—even if that person never showed symptoms.

Table 2.3 Types of SARS-CoV-2 Diagnostic Tests [1-6]

TYPE OF TEST	SPECIMEN	PERFORMANCE CHARACTERISTICS	NOTES
RT-PCR	Respiratory tract	• Sensitivity is 71% to 98% and varies by days post symptoms onset, sampling site, and sample quality	• 30 minutes to 8 hours assay time • Turnaround time variable depending on test and laboratory workflow • Potential for home collection
Antigen	Naso-pharyngeal or Nasal swab	• Less sensitive than RT-PCR tests • Concordance with RT-PCR varies by study and viral load	• < 1-hour assay time • Potential for home testing • Data on use limited
Serology	Blood	• Variable sensitivity and specificity • Antibodies take 1-2 weeks to develop	• 15 minutes to 2 hours assay time • Turnaround time is variable depending on test and laboratory workflow • Unclear or presence of antibodies reduces or eliminates infection risk

Due to global shortage of testing kits and other supplies, and limitation in local capacity for testing, there is a need to rationalize available tests and prioritize groups based on risk/s present in an individual. Hence, three testing strategies are identified: Diagnostic testing, screening testing, and surveillance testing.[7]

Diagnostic testing for SARS-CoV-2 is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with COVID-19, or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Examples of diagnostic testing include testing symptomatic persons, testing persons identified through contact tracing efforts, and testing those who indicate that they were exposed to someone with a confirmed or suspected case of COVID-19.

Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission. Examples of screening include testing in congregate settings, such as a long-term care facility or a correctional facility, a workplace testing its employees, or a school testing its students, faculty, and staff

Surveillance testing for SARS-CoV-2 is intended to monitor for a community- or population-level infection and disease, or to characterize the incidence and prevalence of disease. Surveillance testing is used to gain information at a population level, rather than an individual level, and results of surveillance testing are only returned in aggregate to the requesting institution. Surveillance testing is performed on de-identified specimens, and thus results are not linked to individuals. Surveillance testing does ***not*** involve returning a diagnostic test result to an individual, or for individual decision-making. An example of surveillance testing is a plan developed by a local public health unit to randomly select and sample a percentage of all persons in a city on a rolling basis to assess local infection rates and trends.

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WHAT IS THE GOLD STANDARD IN THE DIAGNOSIS OF COVID-19 INFECTION?

STATEMENT:

Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test is the gold standard to identify COVID-19 infection.

SUPPORTING STATEMENTS:

Thus far, the most commonly used and reliable test for diagnosis of COVID-19 has been the RT-PCR test performed using nasopharyngeal swabs or other upper respiratory tract specimens, including throat swab or, more recently, saliva. Test results are generally available within a few hours to 2 days.

Table 2.4 Detection Rate from Different Biological Sources

Biological sources where severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be detected in coronavirus disease 2019 (COVID-19) patients. (Source: Lippi, et al)	
Biological Source	**Detection Rate (%)**
Bronchoalveolar lavage	>90
Saliva	~90
Sputum	~70
Nasopharyngeal AND Oropharyngeal swabs	~70
Nasal swabs	~60
Pharyngeal swabs	~30
Stool	~30
Throat washing	~30
Blood	15-30
Adapted from: Lippi G, Mattiuzzi C, Bovo C, Plebani M. Current laboratory diagnostics of coronavirus disease 2019 (COVID-19). Acta Biomed. 2020 Apr. 16. Doi: 10.23750/abm.v91i2.9548.	

Furthermore, the accuracy and reliability of RT-PCR for diagnosing SARS-CoV-2 infection depends on many biological and technical variables.[15] Beside the influence of procedures used for collecting, transporting and storing the specimens, as well as from concomitant antiviral therapy,[16] virus detection is largely influenced by the biological source. Wang et al., for example, recently showed that the rate of RT-PCR detection of SARS-CoV-2 in patients diagnosed with COVID-19 is as high as 93% in bronchoalveolar lavage (BAL) fluid, but then decreases to 72% in sputum and 63% in nasal swabs, respectively, whilst it is only 32% in pharyngeal swabs and 29% in stool. To et al. also reported that the positive rate of RT-PCR for SARS-CoV-2 is 15-30% in blood and 14-38% in rectal swabs, respectively.

False-negative result, on the other hand, ranges of 17-63% for nasopharyngeal SARS-CoV2 RT-PCR have been reported in non-pregnant patients; however, without clear gold standard tests available, diagnostic test characteristics including sensitivity, specificity, positive and negative predictive values of SARS-CoV2 RT-PCR assays are difficult to determine.[19-21] Sensitivity of BAL samples appear to be higher than nasopharyngeal or oropharyngeal swabs, but requires invasive and high-risk aerosolizing bronchoscopy to obtain a sample.[20,21]

Given these, the most prudent strategy may be to presume that all patients are infected and use the best available infection prevention possible during the duration of this pandemic.

Then again, there are issues that have arisen with RT-PCR. First, the availability of RT-PCR reagent kits has not kept up with demand. Second, community or provincial hospitals outside of urban cities (NCR or laboratories other than those identified as subnational laboratories) lack the PCR infrastructure to accommodate high sample output. Lastly, RT-PCR relies on the presence of detectable SARS-CoV-2 in the sample collected. If an asymptomatic patient was infected with SARS-CoV-2 but has since recovered, RT-PCR would not identify this prior infection, and control measures would not be enforced. Despite these issues, given the lack of effective vaccines or treatments as of writing, the only currently available lever to reduce SARS-CoV-2 transmission is to identify and isolate persons who are contagious.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

RT-PCR assays have been designed to detect SARS-CoV-2 genetically. RT-PCR involves the reverse transcription of SARS-CoV-2 RNA into complementary DNA (cDNA) strands, followed by amplification of specific regions of the cDNA.[1,2]

RT-PCR is the most predominantly used method for diagnosing COVID-19 using respiratory sample.[8] Upper respiratory samples are broadly recommended, although lower respiratory samples are recommended for patients exhibiting productive cough.[9] Upper respiratory tract samples include nasopharyngeal swabs, oropharyngeal swabs, nasopharyngeal washes, and nasal aspirates. Lower respiratory tract samples include sputum, bronchoalveolar lavage (BAL) fluid, and tracheal aspirates. Both BAL and tracheal aspirates can be high risk for aerosol generation.

The detectable viral load depends on the days after illness onset. In the first 14 days after onset, SARS-CoV-2 could most reliably be detected in sputum followed by nasal swabs, whereas throat swabs were unreliable 8 days after symptom onset.[10] Given the variability in the viral loads, a negative test result from respiratory samples does not rule out the disease. These negatives could result from improper sampling techniques, low viral load in the area sampled, or mutations in the viral genome.[11] Moreover, a “positive” PCR result reflects only the detection of viral RNA and does not necessarily indicate presence of viable virus.[12]

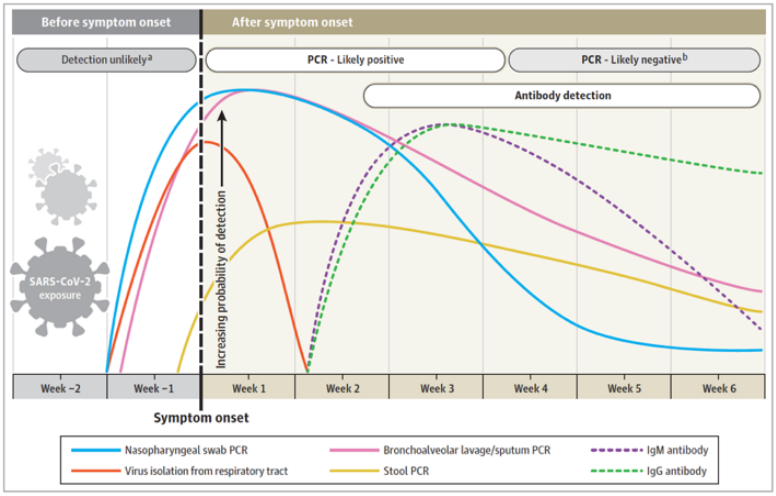

Figure 2.3 Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset (Source: Sethuraman, et al.)

In some cases, viral RNA has been detected by RT-PCR even beyond week 6 following the first positive test.[14] A few cases have also been reported positive after 2 consecutive negative PCR tests performed 24 hours apart. It is unclear if this is a testing error, reinfection, or reactivation. In a study of 9 patients, attempts to isolate the virus in culture were not successful beyond day 8 of illness onset, which correlates with the decline of infectivity beyond the first week. [12] That is in part why the "symptom-based strategy" of the Centers for Disease Control and Prevention (CDC) indicates that health care workers can return to work, if "at least 3 days (72 hours) have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath); and, at least 10 days have passed since symptoms first appeared."[13]

Bronchoscopy

Bronchoscopy helps in obtaining BAL samples in patients who are unable to expectorate sputum for bacterial culture studies, AFB smear, or GeneXpert.[1] It can also be used to clear out mucus plugs in ventilated patients. However, it may cause some deterioration in clinical condition, especially in patients who are on high oxygen support. Likewise, there is high risk of infection transmission to providers resulting from high aerosol production during the procedure. Moreover, there will be significant utilization of valuable resources during bronchoscopy, which will be limited in supply during a pandemic. Hence, bronchoscopy should not be done only for the purpose of ruling COVID-19.[4,5]

If bronchoscopy is warranted, consider the use of a disposable bronchoscope if available. Consider performing bronchoscopy in the patient's place of care to minimize the exposure and contamination. Minimize staff inside the room during procedure; use a negative pressure room if available. Complete personal protective equipment should be used. Standard disinfection protocols should be followed for cleaning your flexible bronchoscopes and video monitors.

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CAN ANTIGEN TEST BE USED IN THE DIAGNOSIS OF COVID-19 INFECTION?

STATEMENT:

Rapid antigen test (AgT) can be used as a substitute for RT-PCR in diagnosing symptomatic cases and asymptomatic close contacts who fit the suspect case definition. It shall be used in settings with insufficient RT-PCR capacity or when results are critical for patient cohort management and quick case finding. Only FDA-certified antigen tests with Health Technology Assessment Council (HTAC) specifications are used.

SUPPORTING STATEMENTS:

Antigen tests are immunoassays that detect the presence of a specific viral antigen, which implies current viral infection. Antigen tests are currently authorized to be performed on nasopharyngeal or nasal swab specimens placed directly into the assay's extraction buffer or reagent.

Antigen tests are relatively inexpensive and can be used at the point-of-care. The currently authorized devices return results in approximately 15 minutes. Antigen tests for SARS-CoV-2 are generally less sensitive than viral tests that detect nucleic acid using reverse transcription polymerase chain reaction (RT-PCR).

The clinical performance of rapid antigen diagnostic tests largely depends on the circumstances in which they are used. Rapid antigen tests perform best when the person is tested in the early stages of infection with SARS-CoV-2 when viral load is generally highest. They also may be informative in diagnostic testing situations in which the person has a known exposure to a confirmed case of COVID-19. Rapid antigen tests can be used for screening testing in high-risk congregate settings in which repeat testing could quickly identify persons with a SARS-CoV-2 infection to inform infection prevention and control measures, thus preventing transmission. In this case, there may be value in providing immediate results with antigen tests even though they may have lower sensitivity than RT-PCR tests, especially in settings where a rapid turnaround time is required.

The "gold standard" for clinical diagnostic detection of SARS-CoV-2 remains RT-PCR. Thus, it may be necessary to confirm a rapid antigen test result with a nucleic acid test, especially if the result of the antigen test is inconsistent with the clinical context. When confirming an antigen test result with a RT-PCR test, it is important that the time interval between collection of samples for the two tests is less than two days, and there have not been any opportunities for new exposures between them. If more than two days separate the two collections, or if there have been opportunities for new exposures, the nucleic acid test should be considered a separate test – not

a confirmatory test. **A positive antigen test in an individual with a high index of suspicion is interpreted as a confirmed case of COVID-19 and should immediately be isolated and managed accordingly. A negative antigen result shall be further confirmed with RT-PCR test.** There are limited data to guide the use of rapid antigen tests as screening tests on asymptomatic persons to detect or exclude COVID-19, or to determine whether a previously confirmed case is still infectious.

For symptomatic close contacts, a positive AgT result shall be treated as the final diagnostic test result. Symptomatic close contacts who tested negative for AgT, as well as asymptomatic close contacts regardless of AgT result, shall undergo confirmatory RT-PCR test.[1,2]

The sensitivity of rapid antigen tests, ranging from 84.0% to 97.6%, is generally lower than RT-PCR. Antigen levels in specimens collected beyond 5-7 days of the onset of symptoms may drop below the limit of detection of the test. This may result in a negative test result, while a more sensitive test, such as RT-PCR, may return a positive result. The specificity of rapid antigen tests, on the other hand, is generally as high as RT-PCR – which means that false positive results are unlikely. Rapid antigen tests should be interpreted in the context of the prevalence of infection or disease, the device's performance characteristics and instructions for use, and the patient's clinical signs, symptoms, and history.

Clinicians should understand antigen test performance characteristics in order to recognize potentially false negative or false positive results and to guide patient management. Laboratory and testing professionals who perform rapid antigen tests should also understand the factors that affect the accuracy of antigen testing.

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IS THERE A ROLE FOR ANTIBODY (SEROLOGY) TESTING IN DIAGNOSING COVID-19?

STATEMENT:

Antibody test results should not be used to diagnose an active COVID-19 infection. Antibodies develop within 1 to 3 weeks after infection. A positive test is presumed to mean that a person was infected with SARS-CoV-2 in the past and does not mean an active infection.

SUPPORTING STATEMENTS:

Serologic assays for SARS-CoV-2, now broadly available, can play an important role in understanding the virus's epidemiology in the general population and identifying groups at higher risk for infection. Unlike direct detection methods such as viral nucleic acid amplification or antigen detection tests that can detect acutely infected persons, antibody tests help determine whether the individual being tested was previously infected—even if that person never showed symptoms. Serologic tests detect resolving or past SARS-CoV-2 virus infection indirectly by measuring the person's humoral immune response to the virus. Therefore, serologic assays do not typically replace direct detection methods as the primary tool for diagnosing an active SARS-CoV-2 infection, but they do have several important applications in monitoring and responding to the COVID-19 pandemic.

Although serologic tests should not be used at this time to determine if an individual is immune, these tests can help determine the proportion of a population previously infected with SARS-CoV-2 and provide information about populations that may be immune and potentially protected. Thus, demographic and geographic patterns of serologic test results can help determine which communities may have experienced a higher infection rate and therefore may have a higher proportion of the population with some degree of immunity, at least temporarily. In some instances, serologic test results may assist with identifying persons potentially infected with SARS-CoV-2 and determining who may qualify to donate blood that can be used to manufacture convalescent plasma as a **possible** treatment for those who are seriously ill from COVID-19.

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WHAT IS THE ROLE OF RADIOLOGIC IMAGING IN COVID-19?

STATEMENT:

The use to radiologic imaging (CXR, chest CT and lung ultrasound) is not recommended as a screening tool in asymptomatic to mild cases. It is indicated in moderate to severe cases of the disease and in cases with deterioration of respiratory function.

SUPPORTING STATEMENTS:

The findings on chest imaging are not specific of the infection, and could overlap with other entities, such as influenza. There are also recommendations about the performance of the chest radiography, including the fact that it is better to avoid the movement of the patient within the hospital.

The value of an imaging test relates to the generation of results that are clinically actionable either for establishing a diagnosis or for guiding management, triage, or therapy. That value is diminished by costs that include the risk of radiation exposure to the patient, risk of COVID-19 transmission to uninfected healthcare workers and other patients, consumption of PPE, and need for cleaning and downtime of radiology rooms in resource-constrained environments.

Chest x-ray (CXR) is insensitive in mild or early COVID-19 infection.[5] However, with respect to the relative value of CXR or computed tomography (CT) for detecting the presence of viral pneumonia, the experience is vastly different dependent upon community norms and public health directives. When patients are encouraged to present early in the course of their disease, as was the case in Wuhan, China, CXR has little value. The greater sensitivity of CT for early pneumonic changes is more relevant in the setting of a public health approach that required isolation of all infected patients within an environment where the reliability of COVID-19 testing was limited and turnaround times were long.[12] Alternatively, in New York City where patients were instructed to stay at home until they experienced advanced symptoms, CXR was often abnormal at the time of presentation. While ultrasound has been suggested as a potential triage and diagnostic tool for COVID-19 given the predilection for the disease in subpleural regions, there is limited experience at this time,[1] as well as infection control issues.

Thoracic imaging using CXR and CT are key tools for pulmonary disease diagnosis and management, but their role in the management of COVID-19 has not been considered within the multivariable context of the severity of respiratory disease, pre-test probability, risk factors for disease progression, and critical resource constraints. To address this deficit, a multidisciplinary panel comprised principally of radiologists and pulmonologists from 10 countries with experience managing COVID-19 patients

across a spectrum of healthcare environments evaluated the utility of imaging within three scenarios representing varying risk factors, community conditions, and resource constraints.[2]

The Fleischner Statement [2]

Written from multidisciplinary and multinational perspectives, the Fleischner Statement is intended to provide context for the use of imaging to direct patient management during the COVID-19 pandemic in different practice settings, different phases of epidemic outbreak, and environments of varying critical resource availability. The consensus statement is structured around **three clinical scenarios and three additional situations** in which chest imaging is often considered in the evaluation of patients with potential COVID-19 infection.

The scenarios apply only to patients presenting with features consistent with COVID-19 infection. The scenarios distinguish mild respiratory disease from moderate-to-severe respiratory disease based on the absence vs. presence of significant pulmonary dysfunction or damage. Pre-test probability is defined by the background prevalence of infection and can be estimated by observed transmission patterns: low by sporadic transmission; moderate by clustered transmission; and high by community transmission.

Scenario 1: Mild Features of COVID-19

The first scenario addresses a patient presenting for evaluation at an outpatient clinic or via telehealth with mild respiratory features consistent with COVID-19 infection, any pre-test probability of COVID-19 infection, and no significant critical resource constraints.

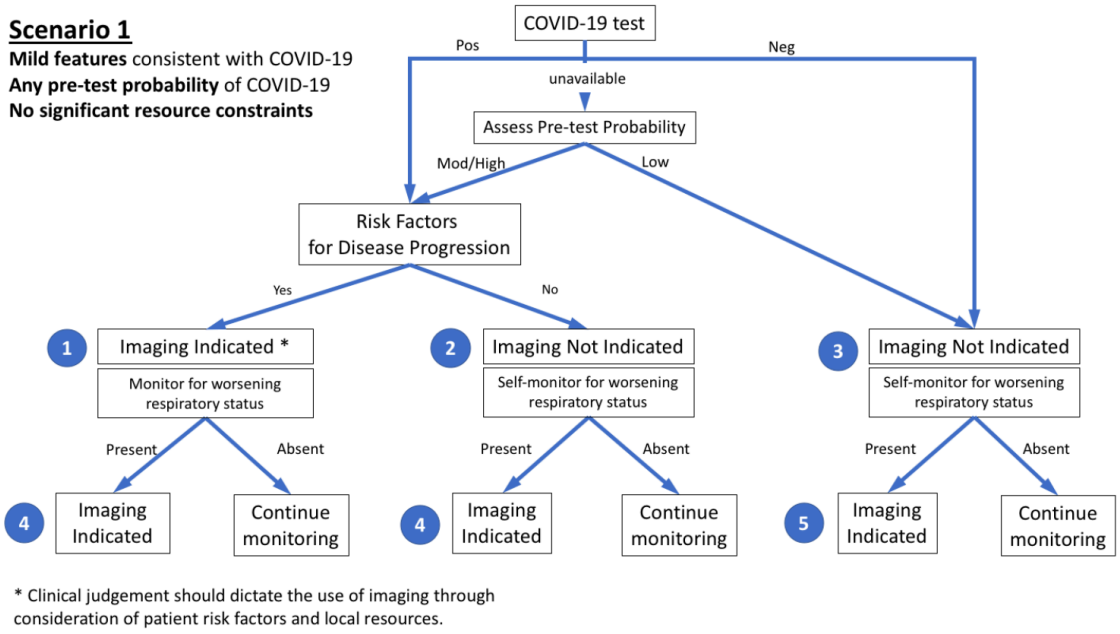

Figure 2.4 Clinical Scenario 1

When COVID-19 test results are unavailable, patients with moderate-to-high pre-test probability should be initially managed as if COVID-19 testing is positive, while patients with low pre-test probability should be initially managed as if COVID-19 testing is negative. Imaging is advised for patients with risk factors for COVID-19 progression and either positive COVID-19 testing or moderate-to-high pre-test probability in the absence of COVID-19 testing. Imaging provides a baseline for future comparison, may establish manifestations of important comorbidities in patients with risk factors for disease progression, and may influence the intensity of monitoring for clinical worsening. Imaging is not advised for patients with mild features who are COVID-19 positive without accompanying risk factors for disease progression, or for patients with mild features who are COVID-19 negative. The panel felt that the yield of imaging in these settings would be very low and that it was safe for most patients to self-monitor for clinical worsening. Regardless of COVID-19 test results and risk factors, imaging is advised for patients with mild clinical features who subsequently develop clinical worsening. In the absence of clinical worsening, management involves support and isolation of patients with positive COVID-19 testing or patients with moderate to high pre-test probability without COVID-19 test results available. Although not specifically addressed by this scenario, in the presence of significant resources constraints, **there is no role for imaging of patients with mild features of COVID-19.**

Scenario 2: Moderate to Severe Features of COVID-19

The second scenario addresses a patient presenting with moderate-to-severe features consistent with COVID-19 infection, any pre-test probability of COVID-19 infection, and no significant critical resource constraints.

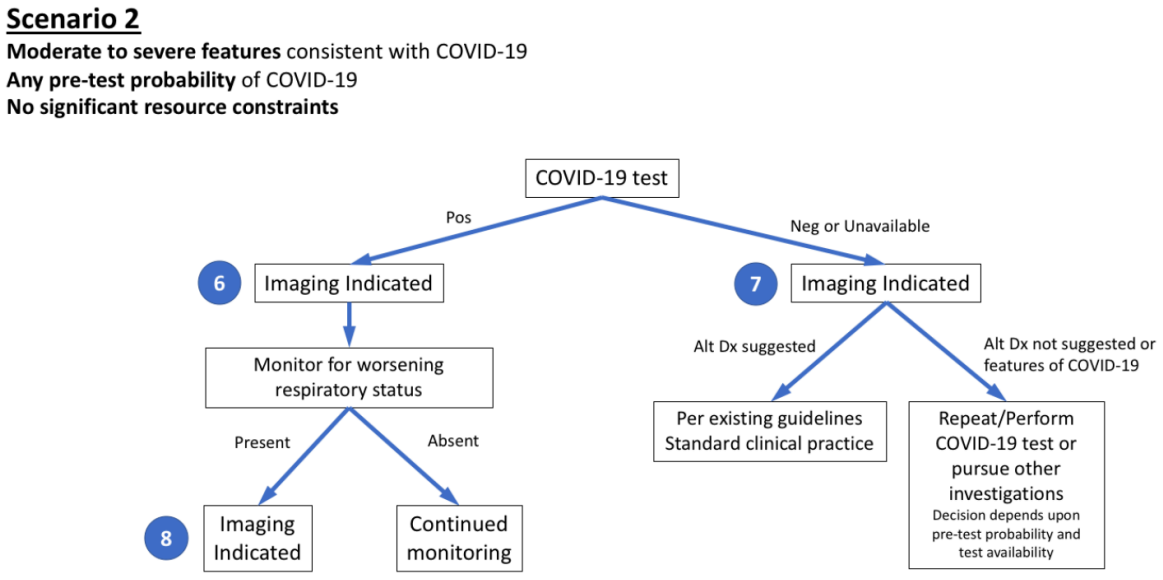

Figure 2.5 Clinical Scenario 2

Imaging is advised regardless of the results or availability of COVID-19 testing given the impact of imaging in both circumstances.

For COVID-19 positive patients, imaging establishes baseline pulmonary status and identifies underlying cardiopulmonary abnormalities that may facilitate risk stratification for clinical worsening. In the presence of clinical worsening, imaging is again advised to assess for COVID- 19 progression or secondary cardiopulmonary abnormalities such as pulmonary embolism, superimposed bacterial pneumonia, or heart failure that can potentially be secondary to COVID-19 myocardial injury.

For COVID-19 negative patients or any patient for whom testing is not performed, imaging may reveal an alternative diagnosis to explain the patient's clinical features, which should direct patent care as per existing clinical guidelines or standard clinical practice. If an alternative diagnosis is not revealed or images demonstrate features of COVID-19 infection, then subsequent clinical evaluation would depend upon the pre-test probability of COVID-19 infection and COVID-19 test availability. False-negative COVID-19 testing is more prevalent in high pre-test probability circumstances and repeat COVID-19 testing is therefore advised if available. Depending upon the imaging findings, other clinical investigations may be pursued.

Scenario 3: Moderate-to-Severe Features of COVID-19 in a Resource Constrained Environment

The third scenario addresses a patient presenting with moderate-to-severe features consistent with COVID-19 infection within an environment of high community disease burden and critical resource limitations (as seen in Wuhan, China, in regions of Italy and Spain, and in New York City, but not in the Philippines, as of yet). Because healthcare personnel and infrastructure may be overwhelmed by a high influx of new patients and resources are limited to provide critical care, urgent decision-making and triage are of primary importance.

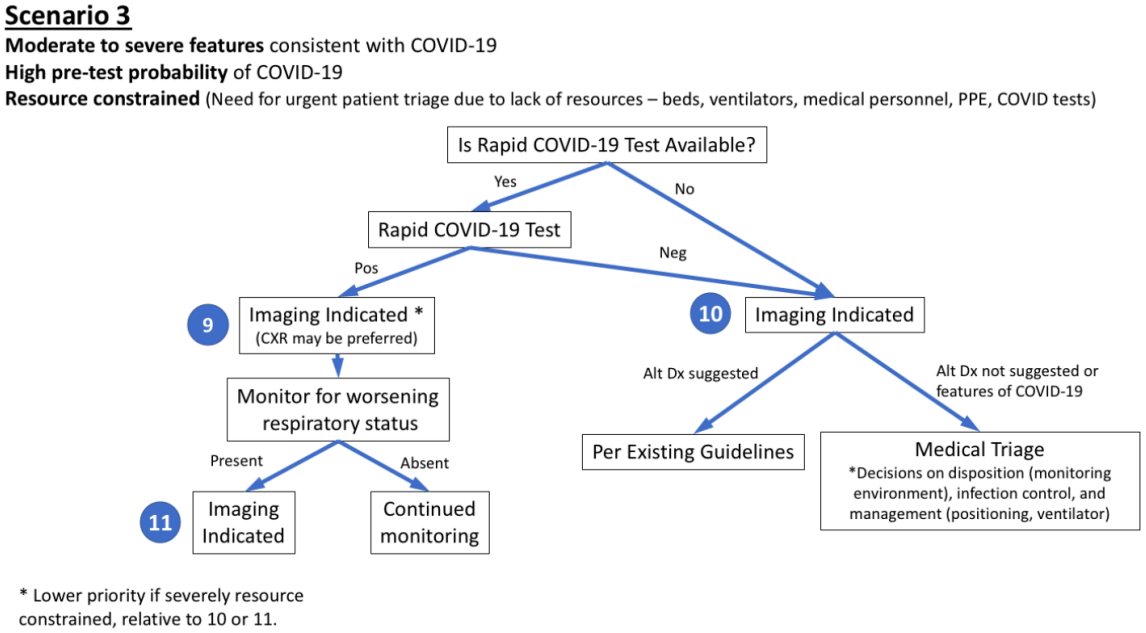

Figure 2.6 Clinical Scenario 3

At the time of this writing, turnaround time for COVID-19 test results range from 3 days (72 hours) to over 7 days. This is an impractically long time period to consider triage to limited hospital beds and ventilators. However, rapid point-of-care (PoC) COVID-19 tests are expected to be released into clinical environments during the first week of April 2020, providing routine turnaround times of less than an hour and potentially as little as 5 minutes. While the initial availability and sample processing capacity of PoC COVID-19 testing is expected to be limited, this should increase over time.

The third scenario first considers the potential availability of PoC COVID-19 testing. Imaging is advised when PoC COVID-19 testing is available and positive for the same reasons as described for Scenario 2. Based upon imaging findings and clinical features, patients are subsequently supported and monitored with a level of intensity consistent with clinical features. Imaging is again indicated if patients subsequently clinically worsen.

Imaging is advised to support more rapid triage of patients in a resource-constrained setting when point-of-care COVID-19 testing is not available or negative. Imaging may reveal features of COVID-19, which within this scenario may be taken as a presumptive diagnosis of COVID-19 for medical triage and associated decisions regarding disposition, infection control, and clinical management. In this high pre-test probability environment, and as described for Scenario 2, the possibility of falsely negative COVID-19 testing creates a circumstance where a COVID-19 diagnosis may be presumed when imaging findings are strongly suggestive of COVID-19 despite negative COVID-19 testing.

This guidance represents a variance from other published recommendations which advise against the use of imaging for the initial diagnosis of COVID-19 and was supported by direct experience amongst panelists providing care within the conditions described for this scenario. The relationship between disease severity and triage may need to be fluid depending upon resources and case load. When imaging reveals an alternative diagnosis to COVID-19, management is based upon established guidelines or standard clinical practice.[4]

Summary of Recommendations for Imaging:

- Imaging is not routinely recommended as a screening test for COVID-19 in asymptomatic individuals.
- Imaging is not indicated for patients with mild features of COVID-19 unless they are at risk for disease progression (*Scenario 1*)
- Imaging is indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results *(Scenarios 2 and 3*)
- Imaging is indicated for patients with COVID-19 and evidence of worsening respiratory status (*Scenarios 1, 2, and 3*)
- In a resource constrained environment where access to CT is limited, CXR may be preferred for patients with COVID-19 unless features of respiratory worsening warrant the use of CT (*Scenarios 2 and 3*)

Chest Radiography (CXR)

The findings on CXR are not specific, and in the initial phases of the disease the studies could be normal. The most common features include lobar, multi-lobar, or bilateral lung consolidation.[3]

Chest Computed Tomography (CT)

CT can play a vital role in the early detection and management of COVID-19.[3,9] However, it is worth emphasizing that a patient with RT-PCR confirmed COVID-19 infection may have normal chest CT at admission. Bernheim et al. reported 20 (56%) of 36 patients imaged 0–2 days after symptom onset had normal CT. Fang et al. reported one of 51 (2%) patient imaged 3 days 6 3 after symptom onset with normal CT. Ai et al. reported 21 of 601 (3%) RTPCR- positive patients with clinical symptoms had normal CT scans.

In contrast, Pan et al. reported four of 21 (19%) patients with first normal CT had lung abnormalities on the follow-up CT approximately 4 days later. Furthermore, Yang et al. reported that among 17 of 149 (11.4%) symptomatic patients with normal chest CT on admission, 12 remained negative 10 days later with two to three follow-up CT examinations and the chest CT of the other five patients became positive over an average of 7 days. **These reports confirm that a normal chest CT scan cannot**

exclude the diagnosis of COVID-19, especially for patients with early onset of symptoms.

Recent studies have reported the features on CT imaging. Pan et al. described the tomographic changes of 21 patients with mild to moderate disease who recovered from the disease, and they described four stages:

- Early stage (0-4 days after the onset of the symptoms), in which ground glass opacities (GGO) are frequent, with sub-pleural distribution and involving predominantly the lower lobes. Some patients in this stage could have a normal CT.
- Progressive stage (5-8 days after the onset of the symptoms), the findings usually evolved to rapidly involvement of the two lungs or multi-lobe distribution with GGO, crazy-paving and consolidation of airspaces.
- Peak stage (9-13 days after the onset of the symptoms), the consolidation becomes denser and it was present in almost all of the cases. Other finding was residual parenchymal bands.
- Absorption stage (>14 days after the onset of the symptoms), no crazy paving pattern was observed, the GGO could remain.

Shi et al. also described the CT findings in 81 patients in Wuhan, China. All of the patients had an abnormal CT, and the features include: GGO, smooth and irregular interlobular septal thickening, crazy paving pattern, air bronchogram and irregular pleural thickening. Usually affecting the subpleural regions and the lower lobes.

Lung ultrasound

The lung ultrasound findings are also not specific for COVID-19 infection. Little information is available to date on this matter. The findings include irregular pleural lines, sub-pleural areas of consolidation, areas of white lung and thick B lines.[14] It is a tool that could be used at bed side avoiding the need for shifting infected patients to a Radiology suite.[8]

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IS REPEAT TESTING WARRANTED AT TERM OR PRIOR TO DELIVERY IN PREGNANT PATIENTS WHO TESTED POSITIVE FOR COVID-19 REMOTE FROM DELIVERY?

STATEMENT:

There is insufficient data to confirm if antibodies protect, what antibody levels are required, or how long will protection last in patients with previous COVID-19 infection. Hence, a repeat testing is warranted to rule out the possibility of a re-infection.

SUPPORTING STATEMENTS:

Generally, immune response to viral infections involves two phases: innate immune response/phase and adaptive immune response/phase 2.

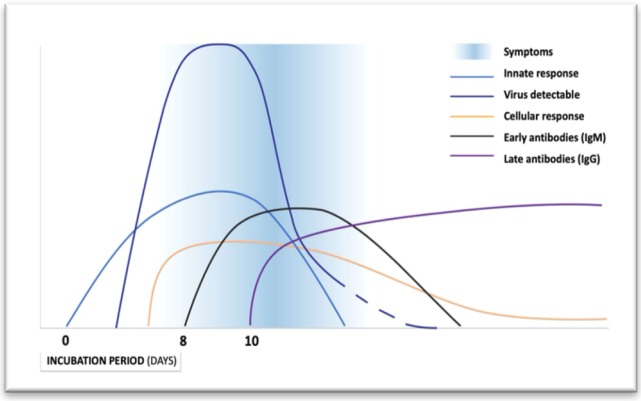

Figure 2.7 The Immune response to viral infections in general [4]

Innate immune response is the general response to ANY infection. Innate immune response cells secrete interferons and other chemicals like cytokines. Interferons and cytokines cause fever, muscle aches, etc. – the early symptoms of infection. Interferons interfere with virus replication. After which, phase 2/adaptive immune response is triggered. A 'weaker' innate response (e.g. in elderly people or those with underlying health problems) may result in delayed stimulation of the adaptive response.

Adaptive immune response is the specific response to the infection which starts 6 to 8 days after the infection. It involves two types of white blood cells: T cells (cellular response) and B cells (antibody response).

T cells (cellular response) recognize cells that are infected with a specific virus and rapidly increase in number to tackle the infection. There 2 types of T cells: 1) CD8+ cytotoxic T cells – kill the cells in which the virus is multiplying and help to slow down or stop the infection, and 2) CD4+ helper T cells – bring in other cells of the immune system and stimulate B-Cells to produce antibodies specific to that virus.

B Cells B (Antibody response) produce antibodies that are specific to that virus. IgM antibodies are produced first and disappear after a few weeks. IgG antibodies are produced at the same time or 2 to 3 days later and titers (levels) usually remain for months or years.

Once the infection is over, the T cells and B cells decline in number, but some cells will remain (memory cells) . Memory cells respond rapidly if they come in contact with the same virus again, killing the virus and accelerating an antibody response.

What do we know about the immune response to COVID-19? Much is still unknown about the immune response of someone who was infected with and recovered from SARS-CoV-2 virus.[1-3]

- Most COVID-19 patients who recovered have antibodies to the SARS-CoV-2 virus detectable in their blood.
- Most COVID-19 patients develop antibodies about 1-3 weeks after symptoms start. This is around the time when many patients start to recover.
- Patients who have had more severe disease appear to have higher levels of important neutralizing antibodies.
- Patients who had mild or asymptomatic COVID-19 have low levels of neutralizing antibodies (or even undetectable levels).
- In these persons it is possible the innate immune response and the T cell response cleared the virus
- Recent studies have shown that neutralizing antibodies may disappear after 3 months

The magnitude of the antibody and T-cell responses can differ and be discordant among individuals and is influenced by disease severity (asymptomatic, mild, moderate, or severe). The immune correlates of protection are not yet defined for COVID-19, but neutralizing antibodies, especially those that recognize the viral receptor binding domain (RBD) and other epitopes on the spike protein that prevent subsequent angiotensin-converting enzyme II receptor binding, membrane fusion, and viral entry, is one path to immunity.[4]

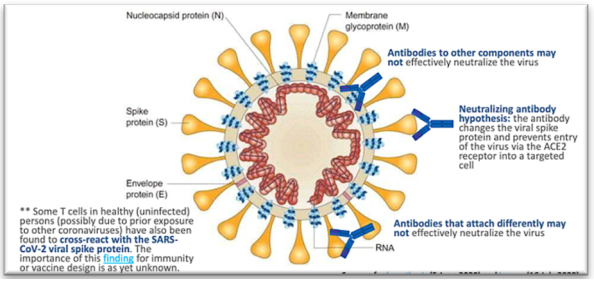

Figure 2.8 Components of the SARS-CoV-2 virus: neutralizing antibodies bind to viral proteins[4]

Recent reports have demonstrated a decline in IgG neutralizing antibodies to SARS-CoV-2 in convalescence, raising apprehension of susceptibility to reinfection. Antibody levels always decline after the acute phase of infection because most of the plasmablasts, the "effector" response of B cells, induced during the first weeks after infection are short-lived. A similar pattern is seen with the effector CD8+ T-cell response. After this reduction, serological memory is then maintained by the smaller number of long-lived plasma cells that reside in the bone marrow and constitutively secrete antibody in the absence of antigen. The antibody recall response comes from this pool of memory B cells that are also long-lived. In fact, rare circulating memory

cells have been shown to produce highly potent neutralizing antibodies when serum neutralizing titers are low.[5] Thus, an early decline of neutralizing antibody levels should not be of concern. The key is at what levels the antibody titers stabilize after natural infection or vaccination. This represents the generation of long-lived plasma cells to protect against subsequent infection.

More than 8 months into the outbreak and after millions of infections globally, **anecdotal case reports** of reinfection mostly after initial mild COVID-19 illness are appearing. Although the complete immune profile of these individuals is not clear, reinfection with SARS-CoV-2 suggests that the natural human immune response may not provide sterilizing immunity but that it may shorten viral shedding, reduce spread, and prevent disease.

Majority reports that recurrence of COVID-19 illness appears to be very uncommon, suggesting that the presence of antibodies could indicate at least short-term immunity to infection with SARS-CoV-2. Consistent with this observation, experimental primary infection in primates and subsequent development of antibodies resulted in protection from reinfection after the primates were rechallenged. Additionally, antibody development in humans correlates with a marked decrease in viral load in the respiratory tract. Taken together, these observations suggest that the presence of antibodies may decrease a person's infectiousness and offer some level of protection from reinfection. However, it remains uncertain to what degree and for how long individuals with antibodies (neutralizing or total) are protected against reinfection with SARS-CoV-2 or what concentration of antibodies may be needed to provide such protection.

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MANAGEMENT OF PREGNANT PATIENTS WITH COVID-19

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ARE PREGNANT PATIENTS AT HIGHER RISK OF GETTING COVID-19?

STATEMENT:

Pregnant women do not appear to have an increased risk of acquiring COVID-19 infection. However, those who are infected seem to be at higher risk for developing severe illness, are more likely to be hospitalized, warrant admission to the intensive care unit (ICU) or require invasive mechanical ventilation.

SUPPORTING STATEMENTS:

Pregnancy generally does not increase the risk of acquiring SARS-CoV-2 infection, but it may worsen the clinical course of COVID-19 compared with non-pregnant individuals of the same age.[1] Recent evidence suggests that pregnant women who get infected with COVID-19 might be at an increased risk of developing severe illness compared to non-pregnant women.

A systematic review and meta-analysis of 77 studies in pregnant and recently pregnant women admitted to the hospital for suspected or confirmed COVID-19 infection showed that compared to non-pregnant women of reproductive age, pregnant patients were more likely to need admission to an intensive care unit (1.62, 1.33-1.96, I^2 = 0%) and require invasive ventilation (1.88, 1.36-2.61, I^2 = 0%).[2] The COVID-19-associated Hospitalization Surveillance Network or COVID-NET, which collects data on hospitalized pregnant women with laboratory-confirmed SARS-CoV-2, reported similar findings. In the report collected from March 1 to August 22, 2020, approximately one in four women aged 15-49 years with COVID-19 was pregnant (598/2255, 26.5%). Among 598 hospitalized pregnant women, 45.5% were symptomatic on admission. Among those who were symptomatic, 16.2% were admitted to an ICU setting and 8.5% required invasive mechanical ventilation.[3] Three other European studies observed comparable findings.[4,5,6] These results elucidate that although there are more asymptomatic COVID-19 pregnant women on admission, a significant proportion of those with symptoms are at an increased

risk of developing severe infections warranting COVID-19-associated hospitalization. Moreover, the high percentage of symptomatic pregnant women admitted to an ICU set-up indicate that outcomes might be more severe among pregnant women admitted with acute illness than among those admitted for obstetric indications alone.[3] However, no increase in the rate of mortality was noted. A meta-analysis of 26 studies showed that mortality rate remains low at 0.1% (73/11,580), from death of any cause among confirmed COVID-19 pregnant patients.[2]

Consistent with the general population with comorbidities developing severe COVID illness, pre-existing maternal comorbidity in pregnant COVID-19 patients was identified as the main risk factor for admission to an intensive care unit (4.21, 1.06 to 16.72; $I^2 = 0\%$) and invasive mechanical ventilation (4.48, 1.40 to 14.37; $I^2 = 0\%$).[2] Comorbidities such as cardiopulmonary disease, chronic kidney disease stage III-IV, immunosuppression, pre-gestational diabetes, HIV infection, or prolonged corticosteroid therapy may increase the risk of developing more severe clinical manifestations.[7] Other risk factors associated with severe COVID-19 in pregnancy include increased maternal age (1.78, 1.25-1.55; $I^2 = 0\%$), high body mass index (2.38, 1.67 to 3.39; $I^2 = 0\%$), chronic hypertension (2, 1.14 to 3.48; $I^2 = 0\%$) and pre-existing diabetes (2.51, 1.31 to 4.8; $I^2 = 0\%$).[2]

Race or ethnicity is another risk factor cited in several investigations. In the study of Ellington and colleagues, it was noted that pregnant women who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection.[8] COVID-NET gathered analogous data showing that a large proportion of hospitalized pregnant patients were Hispanic (42.5%) and Black (26.5%) suggesting that women with this racial and ethnic composition might have higher rates for COVID-19-related hospitalization than women of other race and ethnicity.[2] Although a reason for this may be the long standing inequalities in the social conditions of health, such as occupation and housing circumstances that make physical distancing challenging for some racial and ethnic minority groups at increased risk for COVID-19-associated illness.[9,10]

Evidence suggests that individuals admitted to hospitals with COVID-19 are hypercoagulable. Considering that pregnancy is also known to be a hypercoagulable state,[11] it follows that infection with COVID-19 is likely to be associated also with an increased risk of maternal venous-thromboembolism.[12]

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WHAT ARE THE KNOWN OBSTETRIC COMPLICATIONS OF COVID-19 INFECTION?

STATEMENT:

Preterm birth rates are increased among pregnant women with COVID-19 and their newborn are more likely to be admitted to a neonatal unit. Cesarean section rate is higher compared to general population for iatrogenic reasons.

SUPPORTING STATEMENTS:

A systematic review of maternal and perinatal outcomes involving 11,432 pregnant women and recently pregnant women with suspected or confirmed COVID-19 revealed that the odds of any preterm birth was higher in COVID-infected women than in those without the disease (3.01; 95% confidence interval (CI) 1.16-7.85; I^2 = 1%). Majority of these preterm deliveries were iatrogenic (94%) and spontaneous preterm birth was observed in 6% of cases (95% CI 3-3%; I^2 =55%). A quarter of all neonates born to these mothers were admitted to the neonatal unit with an increased risk of admission (odds ratio 3.13, 95% CI,2.05-4.78) than those born to mothers without COVID-19.[1] The same findings were observed by the COVID-Associated Hospitalization Surveillance Network (COVID-NET), which collects data on hospitalized pregnant women with laboratory-confirmed SARS-COV-2. In this study, the prevalence of preterm delivery among livebirths in 598 COVID-19-associated hospitalization was 12.6%, which was higher than the 10% rate observed in the general population in the US in 2018. They have also noted that preterm birth occurred approximately three times more frequently in symptomatic pregnant women (23%) than in those who were asymptomatic (8%). [2] In another study that specifically reported outcome by disease severity, birth was preterm in 9 percent of women with severe disease and 75% in those with critical.[3]

The frequency of spontaneous abortion does not appear to be increased, but data on first trimester infections are limited.[4,5] In the US, the stillbirth rate among hospitalized pregnant patients is approximately 3%.[2,6]

Cesarean delivery rates were notably increased in many investigations. In the study by Allotey et al., 65% of deliveries was by cesarean while the overall rate of Cesarean section reported by COVID-NET was 33%, 42% in symptomatic and 29% in asymptomatic mothers.[1,2] It appears that many of the third trimester cases are electively delivered by cesarean section because of a bias to intervene, catalyzed by the belief that management of severe maternal respiratory disease would be improved by delivery. However, this assumption remains to be proven.[4]

Intrauterine fetal growth restriction (IUGR) has so far not been reported in association with COVID-19 infection. Although IUGR is a known consequence of chronic maternal hypoxia, the effects of shorter and transient hypoxia in COVID-19 are unknown. During the SARS-epidemic in 2003, small for gestational age

neonates were reported in two women contracting the infection at 28 and 30 weeks of gestation and delivering at 33 and 37 weeks respectively.[7] In reported COVID-19 patients, delivery generally occurred within one week of diagnosis, making it impossible to assess the long-term effect of transient maternal hypoxemia on fetal growth.[8-11]

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CAN COVID-19 INFECT THE FETUS IN-UTERO?

STATEMENT:

Vertical transmission of SARS-CoV-2 is possible and seems to occur in a minority of cases of COVID-19 infection in the third trimester.

SUPPORTING STATEMENTS:

As more and more pregnant women are being infected with COVID-19 globally, the potential for mother to child SARS-CoV-2 transmission has been of utmost concern to clinicians worldwide. Initial reports from China suggested that intrauterine transmission was unlikely. [1] However, cases of possible vertical transmission during third trimester infection are continuously being reported. Fortunately, most babies who become infected are asymptomatic or exhibit mild symptoms at birth.[2]

A systematic review of 30 eligible case reports describing 956 tested neonates of COVID-19 infected women revealed that 27 neonates had a positive result for SARS-CoV-2 viral RNA test using nasopharyngeal swab, indicating a pooled proportion of 3.2% (95% CI, 2.2-4.3) for vertical transmission. This study also reported that viral RNA testing was positive in 2.9% of neonatal cord blood samples (1/34), 7.7% of placenta samples (2/26) and 9.7% of fecal or rectal swabs (3/31). No urine nor amniotic fluid samples tested positive for viral RNA in this review. Neonatal serology was positive in 3.7% of cases (3/82), based on the presence of immunoglobulin M (IgM). [3] However, vertical transmission can be antenatal or intrapartal and the initial case reports were unable to ascertain whether infection occurred in utero or during delivery.

Intrapartum infection can occur through exposure of the infant to infectious virus in maternal blood or secretions during the birth process. As SARS-CoV-2 has been detected in feces and vaginal secretions, this is a possibility in some of the reported cases.

For in-utero transmission to occur, the pathogen must be present in the blood and able to cross the placenta to infect the uterus. If viremia occurs, allowing the virus to reach the placenta, the presence of ACE-2, the SARS-CoV-2 receptor, in both placenta and fetal tissues suggest transplacental passage and infection may be possible. The observation that viremia secondary to SARS-CoV-2 is uncommon contributes to the low probability of antepartal or in-utero transmission.[4] Detection of SARS-CoV-2 IgM antibody in the neonate has been proposed as potential evidence of intrauterine infection since maternal IgM does not cross the placenta. However, IgM assays are not reliable and are prone to both false positive and false negative results owing to cross-reactivities with non-specific IgM antibodies. [4, 5]

Recently, the use of integrated immunohistochemical, electron microscopy and molecular analysis of the fetal side of the placenta, correlated with the

nasopharyngeal swab test obtained by 24 hours of life and development of symptoms compatible with COVID-19 in the neonate are being utilized as evidence of intrauterine infection.[4] Using these parameters, three reported transplacental transmission cases in the newborn of a COVID-19 pregnant women are considered highly probable. One case was described by Fachetti and colleagues in their study of 101 women whose placentas were screened for SARS-CoV-2 spike proteins (S & N). SARS-CoV-2 S and N proteins were strongly expressed in the placenta of a COVID-19-infected woman whose newborn tested positive for viral RNA and developed COVID pneumonia soon after birth. SARS-CoV-2 antigens, RNA and/or particles morphologically consistent with coronavirus were identified in villous syncytiotrophoblasts, endothelial cells and fetal intravascular mononuclear cells suggesting the passage of SARS-CoV-2 across the maternal-fetal interface to infect the fetal-derived cells of the placenta. [6] Another well-documented case of a probable transplacental transmission was demonstrated by Vivanti and colleagues in their case report of a neonate born to a mother infected in the last trimester. The transmission was confirmed by comprehensive virological and pathological investigations detailing that SARS-CoV-2 infected the fetus through a maternal viremia followed by placental infection demonstrated by immunohistochemistry with very high viral load, placental inflammation and finally, neonatal viremia. This neonate was resuscitated at birth, extubated after 6 hours, developed poor suck, irritability and neurologic symptoms on the third day of life but eventually recovered.[7] Sisman, et al. in a published case report demonstrated a third possible intrauterine SARS-CoV-2 infection in a neonate with findings of a positive nasopharyngeal swab obtained by 24 hours of life, strengthened by unequivocal histologic, immunohistochemical and electron microscopic findings on the fetal side of the placenta and the development of a febrile respiratory illness compatible with COVID-19.[8]

Indeed, confirmation of vertical transmission is challenging and require tedious sampling of appropriate tissues and fluid at the time of delivery. Case definitions to define and delineate in-utero versus intrapartum transmission rely on timing of maternal illness relative to delivery, virologic testing of specimens at birth including placenta, amniotic fluid, vaginal secretion, neonatal blood and other secretions plus the development of COVID-related symptoms in the newborn. SARS-Cov-2 in-utero transmission may be rare and difficult to confirm, but it is possible.

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SHOULD CORTICOSTEROIDS BE GIVEN TO PREGNANT WOMEN IN PRETERM LABOR WITH COVID-19 INFECTION?

STATEMENT:

Pregnant women with COVID-19 infection at 24 to 33 6/7 weeks age of gestation should be given corticosteroids. It should be given to those requiring oxygen therapy and/or mechanical ventilation at any age of gestation.

SUPPORTING STATEMENTS:

The American College of Obstetricians and Gynecologists (ACOG) recommends offering antenatal corticosteroids to suspected or confirmed COVID-19 pregnant women between 24 weeks and 33 6/7 weeks gestation who are at risk of preterm birth within 7 days, the same guidelines as for non-COVID patients.[1,2] For pregnancies between 34 and 36 6/7 weeks gestation at risk of preterm birth, antenatal corticosteroids may not be offered since benefits for this group are less well-established. However, this may be individualized based on clinical scenario.[2] Likewise, the Royal College of Obstetricians and Gynecologists (RCOG), Society of Obstetricians and Gynecologists of Canada (SOGC) and Queensland Health also recommend that antenatal corticosteroids for fetal maturation be given as indicated.[3-5]

The benefits of corticosteroids in promoting fetal lung maturity in preterm labor have long been established in the field of obstetrics. This practice was initially challenged by previous observations that corticosteroid use has been associated with increased morbidity and mortality in COVID-19 positive patients. This includes studies by Guan and Shang in China, which showed that outcomes were worse for COVID-19 patients who received corticosteroids.[6,7]

However, the recently completed open-label randomized controlled trial comparing different treatment modalities with usual care in hospitalized patients with COVID-19 – RECOVERY (Randomised Evaluation of COVID-19 Therapy Trial), suggests that patients with COVID-19 who received dexamethasone showed significant reduction in 28-day mortality.[8] Greatest benefit was seen among patients receiving invasive mechanical ventilation followed by patients receiving supplemental oxygen. The NIH COVID-19 treatment guidelines now includes the use of dexamethasone in the management of patients receiving oxygen support.[9] Both RCOG guidelines and RECOVERY Trial recommended use of intravenous hydrocortisone 40mg or oral prednisone 80mg given twice daily for pregnant and breastfeeding patients with COVID-19.[8,10] However, the ACOG recommends the use of methylprednisolone 30mg per day either orally or intravenously because of its limited placental transfer and efficacy in acute lung injury.[11]

For pregnancies between 34 and 36 6/7 weeks gestation at risk of preterm birth, antenatal corticosteroids may not be offered since benefits for this group are less well-established. However, this may be individualized while weighing the benefits and risks for both mother and baby.[2] Corticosteroid use for fetal maturity are not without complications. Repetitive doses of antenatal glucocorticoids have been associated with adverse neurologic outcomes, small head circumferences, fetal growth restriction and increased risk for neonatal hypoglycemia.[12,13]

Women who are not candidates for use of corticosteroids for lung maturity may be given methylprednisolone for the entire duration of 10-day steroid course. However, for COVID-19 confirmed cases, requiring oxygen therapy or mechanical ventilation and at risk of preterm birth, the standard regimen of dexamethasone 6 mg IM every 12 hours for four doses should be given for lung maturity followed by completion of COVID-19 steroid course with methylprednisolone for the next 8 days.[11] Data on the use of dexamethasone during postpartum and in breastfeeding women and its effect on the neonate is limited. Thus, the ACOG current summary instead recommends the use of methylprednisolone 32mg tablet daily to complete 10 days.[11]

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WHEN IS THE BEST TIME TO DELIVER A PREGNANT PATIENT WITH COVID-19 INFECTION?

STATEMENT:

COVID-19 infection alone is not an indication for pregnancy termination. Decisions regarding delivery timing must be individualized. Pregnancies should be allowed to continue until term if women can be successfully treated. The indications for early delivery depend upon the mother's clinical status, gestational age, and fetal well-being.

SUPPORTING STATEMENTS:

There is little data as to the best timing of delivery amongst pregnant women affected by COVID-19 infection making the decision for delivery in the setting of severe COVID-19 infection more challenging. In the absence of strong data, it is important to make decisions based on clinical judgment and with common sense, hopefully, with the least adverse effects on the maternal and neonatal outcomes.

The increased oxygen consumption and reduced functional residual capacity of pregnancy predispose to rapid deterioration of both maternal and fetal status when combined with the pathologic changes associated with severe infection. The decision for delivery should be based on the gestational age, maternal status, and fetal status. Importantly, stabilizing the mother prior to emergent delivery for fetal indications is imperative. Through stabilization of the mother, the fetus' status will likely improve.[1]

For most women with preterm COVID-19 and non-severe illness who have no medical/obstetric indications for prompt delivery, delivery is not indicated and ideally should occur sometime after a negative testing result is obtained or isolation status is lifted, thereby minimizing the risk of postnatal transmission to the neonate.[2]

In women with severe illness, there are multiple issues to consider, and timing of delivery needs to be individualized.[2,3] Whether the mother's respiratory disease will be improved by delivery, or the risk of postnatal transmission in the delivery room is increased when maternal symptoms are acute are both unclear. It should also be noted that maternal antibody production and in turn, passive newborn immunity may not have had time to develop. On the other hand, increased oxygen consumption and reduced functional residual capacity, which occur during pregnancy, may facilitate maternal deterioration in patients with pneumonia.[4] Excessive uterine distention from multiple gestation or severe polyhydramnios in the third trimester may further compromise pulmonary function.

Table 3-1. Indications for Delivery with Severe COVID-19 Infection

MATERNAL INDICATIONS	FETAL INDICATIONS
▪ Intrauterine infections ▪ Disseminated intravascular coagulation ▪ Hepatic or renal failure ▪ Compromised cardiopulmonary function due to uterine overdistention or presence of peritoneal fluid ▪ Compartment syndrome ▪ Severe ARDS ▪ Cardiopulmonary arrest	▪ Fetal demise ▪ Gestational age associated with low neonatal morbidity or mortality

Adapted from: General Guidelines in the Management of an Obstetrical Patient on the Labor and Delivery Unit during COVID-19 Pandemic. (Stephens AJ, Barton JR, Bentum NA, Blackwell Sc, Sibai BM, Am J Perinatol, Published online: 2020-04-28)

Clinical scenarios, for which delivery is likely indicated to maximize resuscitative efforts in cases of severe COVID-19 complicated by sepsis and septic shock, are presented in Table 3-2. Of note, uterine distention secondary to multifetal gestations, macrosomia, and polyhydramnios among other conditions can result in compromised cardiopulmonary function due to diaphragm displacement. In such patients with compromised cardiopulmonary dysfunction that requires intubation, delivery at 32 weeks should be considered and decision should be balanced with the benefits of pregnancy continuation following consultation with neonatology.

Timing of Delivery for Preterm Prelabor Rupture of Membranes (32-34 weeks)

The potential benefits of additional in-utero time for preterm prelabor rupture of membranes (PPROM) must be balanced in light of current COVID-19 pandemic circumstances and known adverse outcomes in patients with PPROM such as chorioamnionitis, placental abruption, cord prolapse, cord compression, or uteroplacental insufficiency.[5]

Despite the recent randomized control trial of singletons between 34 0/7 and 36 6/7 weeks with PPROM by Morris et al. demonstrating no increased risk of neonatal sepsis or composite neonatal morbidity (sepsis, mechanical ventilation ≥24 hours, stillbirth, or neonatal death), in the current setting, however, there are additional risks associated with extended hospital stays to be considered for patients.

Additionally, this trial also demonstrated increased maternal morbidity, such as hemorrhage and infection, associated with expectant management of PPROM after 34 weeks that would further increase exposure to different medical personnel, movement between different hospital settings (i.e., labor, operating room, and intensive care unit), and overall length of stay.[6]

The potential benefits of expectant management beyond 34 weeks may be diminished by the development of associated adverse outcomes and continued hospitalization during the COVID-19 pandemic.[6-8]

For the hospitalized patient with COVID-19 with pneumonia but not intubated, some authorities[9-11] have advocated consideration of delivery in pregnancies >32 to 34 weeks. The rationale is that delivery is performed before the pulmonary situation worsens and ongoing maternal hypoxemia places the fetus at risk of compromise. Most authorities do not advocate delivery prior to 32 weeks, even though the maternal situation may worsen in the second week, given the known morbidity and mortality of very preterm infants.[12]

Timing of delivery of the hospitalized pregnant woman who is intubated and critically ill with COVID-19 is challenging. After 34 weeks, some have advocated delivery if the patient is stable, but this could exacerbate the maternal condition. Between 32 to 34 weeks age of gestation, continuing maternal support with fetal monitoring is usually suggested for perinatal benefit as long as the maternal situation remains stable or improving. In some situations, maternal extracorporeal membrane oxygenation (ECMO) may be necessary.[13]

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SHOULD INDUCTION OF LABOR BE INSTITUTED FOR PREGNANT WOMEN WITH COVID-19 INFECTION?

STATEMENT:

The decision to do induction of labor in patients with COVID-19 infection is dependent on several factors which include patient's clinical presentation, presence of co-morbid illness/es, internal examination findings (Bishop's score) and hospital bed capacity. As exposure time between patients and healthcare providers are increased with induction of labor, the risks and benefits must be weighed and contemplated by the clinician when considering this procedure.

SUPPORTING STATEMENTS:

COVID-19 is not an indication to alter the route of delivery and cesarean delivery is still performed only for standard obstetric indication even in these patients.[1] Induction of labor is an option which may be offered and considered in the intrapartum care of asymptomatic COVID-19 positive women with medical or obstetric indications.[2] The indications for induction of labor are the same as those for non-COVID pregnant women and includes induction at 39 weeks age of gestation,[4] post-term pregnancies, patients with co-morbidities (hypertensive disorders or diabetes), oligohydramnios, severe fetal growth restriction, prelabor rupture of membranes and those with favorable Bishop's scores.[5] On the other hand, a poor Bishop's score or a clinically unstable patient may be reasons not to consider this procedure. Symptoms were observed to be more severe in the second week of illness therefore planning delivery before this time is optimal.[1,2] Appropriate counselling should be given to these patients prior to induction since the situation being considered among COVID-19 positive patients is that their condition may worsen over time. Likewise, in extreme healthcare system burden, it may be appropriate to consider postponing or re-scheduling induction of labor.[2]

The drawbacks of induction of labor, as elucidated in the study by Grobman and colleagues entitled "A Randomized Trial of Induction Versus Expectant Management" (ARRIVE), were the notable increase in the time of delivery and length of stay in the hospital of patients undergoing this procedure.[3] An extended induction, even with successful vaginal delivery, increases exposure time between patients and the healthcare delivery team. To address this concern, the Royal College of Obstetricians and Gynecologists (RCOG) suggested that certain service modifications may be done to decrease exposure and prevent viral transmission between patients and their relatives and hospital staff. One of their proposals is to reduce induction of labor in cases that are not medically-indicated.[6] Another proposal to limit in-hospital time of these patients, is by utilizing improved outpatient protocols of induction of labor such as the use of cervical ripening agents like oral misoprostol (25 mcg initially followed by 25 mcg every 2-4 hours or 50 mcg every 4-6 hours) or, outpatient Foley bulb cervical ripening (i.e. 60 to 80 mL single balloon

Foley for 12 hours). These may be resorted to, in low-risk COVID-19 positive women, to minimize contact.[3,6]

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WHAT IS THE MODE OF DELIVERY FOR A PREGNANT WOMAN WITH COVID-19 INFECTION?

STATEMENT:

The mode of delivery should be individualized based on standard obstetric indications. COVID-19 is not an indication to change the route of delivery. Vaginal deliveries can be attempted, and cesarean section is performed if clinically warranted.

SUPPORTING STATEMENTS:

According to WHO, the mode of delivery in a pregnant woman with COVID-19 infection should be individualized based on standard obstetric indications.[1] Currently, there is no evidence to favor one mode of birth over another, therefore, the manner of delivery should be discussed with the woman, taking into consideration her preferences and the existing obstetric condition.[2] Thus, for these women, vaginal delivery can be attempted and cesarean section should only be performed when medically warranted.[1,2]

The presence of COVID-19 infection in a pregnant woman is not an indication to change the route of delivery.[1,5,6] In fact, the mode of birth should not be influenced by a positive SARS-CoV-2 result unless the woman's respiratory condition demands an urgent intervention.[2,7,8] Furthermore, a positive SARS-CoV-2 result but stable condition is not even an indication to expedite birth.[8] As such, decisions for the timing and mode of delivery should be individualized, mainly depending on the severity of maternal condition, gestational age and fetal condition.[1,9]

Whenever possible, an operative vaginal delivery should be performed to avoid maternal exhaustion and unnecessary surgical complications in a symptomatic woman who is becoming hypoxic.[2,10]

In a systematic review of nineteen studies involving 79 women infected with coronavirus (SARS, MERS and COVID-19), a diagnosis of pneumonia was made in 91.8% of cases. The most common symptoms were fever (82.6%), cough (57.1%), and dyspnea (27.0%). Eighty four percent (84%) of the pregnant women were delivered by cesarean birth. The study concluded that COVID-19 infection was associated with a relatively higher rate of preterm birth, pre-eclampsia, cesarean delivery, and perinatal death. There have been no published cases of clinical evidence of vertical transmission.[12] But according to Berghella, even if vertical transmission is confirmed in more recent data, this would not be an indication for cesarean delivery since it would only increase maternal risk and would unlikely improve neonatal outcome. Reports of COVID-19 infection in the newborn have been generally described as mild disease.[6]

When there is existing maternal and/or fetal compromise, an emergency delivery must be performed. A prompt cesarean birth is advised for maternal indications, such as septic shock, acute organ failure or any worsening condition of the mother related to COVID-19, or fetal indications, such as non-reassuring fetal status.[10,13] In some cases, critical decisions are made whether to perform an emergency cesarean delivery or to proceed with an induction of labor, as it is done in other maternal emergencies such as severe pre-eclampsia.[2]

During COVID-19 infection, the threshold for cesarean delivery should be lower than usual so that infection control procedures can be readily adhered to, in order to minimize disease transmission.[13] Donning of PPE is time consuming and may have impact on the time of decision until delivery.[2] Locally, there are settings where the facility has no capacity for containing significant exposure on their health workers. Expert opinion for these cases suggests that delivery should be expedited for patients in active labor and have not delivered within two hours.

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SHOULD ANESTHESIA BE GIVEN TO PREGNANT WOMEN WITH COVID-19 DURING DELIVERY?

STATEMENT:

Neuraxial anesthesia (epidural, spinal or caudal) is preferred. Inhalational or general anesthesia should be avoided.

SUPPORTING STATEMENTS:

In patients with known or suspected COVID-19, neuraxial anesthetic (such as spinal, caudal or epidural anesthesia) is not contraindicated and has several advantages in laboring patients. It provides analgesia and reduces cardiopulmonary stress from pain and anxiety which, in turn, decreases chance of viral dissemination. Epidural anesthesia is recommended early in labor to women with suspected or confirmed COVID-19 to minimize the need for general anesthesia if urgent delivery is needed.[1] It has been shown to be safer than general anesthesia (GA) even in COVID-19 pregnant patients because GA poses a greater risk for atelectasis and ICU admission due to decreased respiratory functional capacity. More importantly, intubation and extubation during general anesthesia are considered aerosol-generating procedures which may contribute to spread of the virus and should therefore be avoided in COVID-19 pregnant patients.[1,2]

Literature review of confirmed COVID-19 pregnant patients who underwent neuraxial anesthesia during labor showed that it is safe and no neurologic sequelae nor adverse maternal neurologic events were reported in 77 cases.[3] With epidural anesthesia in place early during labor, it is readily available in case there is a need to do emergency cesarean delivery, obviating the need for GA.[4] However, some authors advise against this routine practice of early epidural insertion during labor for COVID-19 patients citing a 2.5 times increased risk of intrapartum pyrexia with this procedure in general, which can complicate the clinical picture and subsequent management of these patients.[5] For this reason, the decision to do early insertion should be individualized and not routinely done.

The Society of Obstetric Anesthesia and Perinatology suggests suspending the use of nitrous oxide for labor analgesia because of insufficient data about cleaning, filtering and potential aerosolization of nitrous oxide system.[6] Limiting the use of intravenous, patient-controlled analgesia is also advised because of the risk of respiratory depression in COVID-19 patients.[4] Unplanned conversion from regional to general anesthesia (GA) should be avoided if at all possible but should GA be really warranted in these patients, Level 4 PPE must be worn by all involved healthcare providers during such cesarean delivery.[4,7]

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CAN ESSENTIAL INTRAPARTUM AND NEWBORN CARE (EINC) BE INSTITUTED IN DELIVERIES WITH COVID-19 INFECTION?

STATEMENT:

The decision whether or not to perform the four time-bound interventions of EINC should be done on a case to case basis. EINC remains to be the most effective way to protect the newborn. The mother should be advised to strictly follow proper hand hygiene, cough etiquette, wearing of medical mask and disinfection of often-touched surfaces as infection prevention and control measures.

SUPPORTING STATEMENTS:

Essential Intrapartum and Newborn care (EINC) is a package of evidence-based practices recommended by the Department of Health, PhilHealth, and the WHO as the standard of care in all births by skilled attendants in all government and private settings.

EINC practices for newborn care constitute a series of time-bound, chronologically-ordered standard procedures that a baby receives at birth. At the heart of the protocol are four time-bound interventions: immediate drying, skin-to-skin contact followed by clamping of the cord after 1-3 minutes, non-separation of the baby from the mother, and breastfeeding initiation.

The United Nations Children's Fund (UNICEF), the World Health Organization (WHO), the United Nations Population Fund (UNFPA), and World Food Programme (WFP) called on those involved in the response to the COVID-19 pandemic in the Philippines to emphasize that the most effective way to save newborn lives is still through the practice of Essential Intrapartum and Newborn Care (EINC, or "Unang Yakap") and the promotion and protection of breastfeeding while strictly following precautions for infection prevention and control (IPC). The agencies further added that "as with all confirmed or suspected COVID-19 cases, symptomatic mothers who are breastfeeding or practicing skin-to-skin contact or kangaroo mother care should observe hand hygiene and basic IPC measures". When performing skin-to-skin contact, breastfeeding, and any activities involving touching or being close to the baby, infected mothers must use a medical mask, wash their hands properly before and after contact with the child, and routinely clean and disinfect surfaces which the mother has touched.

ACOG has stated that delayed umbilical cord clamping is highly unlikely to increase the risk of transmitting pathogens from an infected mother to the fetus; however, many institutions have chosen to prohibit this practice in term infants, in whom the benefits are modest, to minimize newborn exposure to any virus in the immediate environment and reduce the chances that the newborn will require phototherapy for jaundice.[1] Many institutions also prohibit skin-to-skin contact in these cases,[2]

although the World Health Organization has not advised against this.[3] One expert group suggested leaving the vernix caseosa in place for 24 hours after birth since it contains antimicrobial peptides,[4] whereas the American Academy of Pediatrics advised bathing newborns as soon as reasonably possible after birth to remove virus potentially present on skin surfaces.[5]

It cannot be denied that during emergency situations, the rates of disease and death among babies and children are higher than for any other age group. The younger the child, the higher the risk, leaving babies under six months most vulnerable. Babies who drink formula from an unsterile bottle or teat, or made with unclean water, can become very sick with diarrhea and die within a few hours. Mortality is particularly high, when there is a prevalence of communicable diseases and diarrhea, combined with high rates of undernutrition.

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CAN MOTHERS WITH COVID-19 INFECTION BREASTFEED THEIR INFANTS?

STATEMENT:

Guidelines from WHO and other international societies recommend that mothers who are suspected or confirmed to have COVID-19 infection should be allowed to have skin-to-skin contact and to breastfeed their infants as long as infection control precautions such as strict hand hygiene, use of surgical facemasks, and frequent disinfection are observed. For mothers who are too ill to breastfeed, expression of breastmilk is an option. The decision whether or not to breastfeed ultimately depends on the patient and her family after being informed of the benefits and risks of breastfeeding during COVID-19 infection.

SUPPORTING STATEMENTS:

Breastfeeding has been known to protect the mother and child and its health benefits are evidence-based and remain to be undisputed.[1] Breastfeeding offers immunological protection to the baby. Breastmilk is a passive source of antibodies and anti-infective factors that increase the infant's immunity against infectious diseases. Breastfeeding also reduces the risk of sudden infant death syndrome (SIDS), pneumonia, gastroenteritis, otitis media and other life-threatening diseases.[2]

The risk of coronavirus transmission during breastfeeding is through respiratory droplets or intimate contact.[3] Thus, safe breastfeeding should be encouraged according to standard infant feeding guidelines and mothers with known or suspected COVID-19 should adhere to standard and contact precautions and comply with the recommended hygiene measures during breastfeeding.[4]

Although first reports of the Chinese experience in the management of newborns and mothers with SARS-CoV-2 infection did not recommend mother-baby contact or breastfeeding, international societies such as the WHO and UNICEF promote breastfeeding as long as adequate infection control measures are followed.[5,6,7] In cases where maternal health condition does not allow for breastfeeding, expressing breastmilk and safely providing it to the infants is encouraged.[1,8]

Current evidence states that the Coronavirus is not transmitted via breastmilk but a case report in China showed evidence of viral shedding in breastmilk. In the report by Zhu et al., they noted SARS-CoV-2 RNA positivity in the breastmilk of one (20%) out of five COVID-19 positive mothers. The breastmilk sample was positive after delivery and remained positive for two and three days after. The Ct value of RT PCR test results was relatively high, suggesting the persistent presence of SARS-CoV-2 in human breastmilk of the said COVID-19 patient. This study, however, was retrospective and limited by a small sample size. Even so, the data presented still raises concerns on the risks of transmission to the neonate. The possibility of a

dynamic presence of SARS-COV-2 in breastmilk seen in this study and the confirmation of live, replication-capable virus in breastmilk should be taken into consideration by the clinician when advising breastfeeding to patients.[2]

If the parents and family choose to breastfeed, they should understand that the mother can infect her infant during breastfeeding. The risk of infecting the baby while breastfeeding can be lowered if:

1) The mother is separated from her baby except when breastfeeding. She should be at least 2 meters away from the baby with a curtain between them.
2) The mother wears a well-fitting medical mask at all times when near her baby or other household members.
3) She practices handwashing with soap and water prior to touching her baby and breastfeeding, and she practices regular body hygiene (e.g. takes daily showers).
4) She follows cough etiquette.
5) Her baby is not exposed to the sick mother's respiratory and stool secretions.

If the parents and family decide not to breastfeed, or if the mother is too ill to breastfeed, in order to reduce COVID-19 transmission to the infant:

1) The infant is separated from the mother until the mother is no longer infectious (at least 2 meters apart, with a curtain separating them).
2) If the mother will not breastfeed, infant feeding options include mother's own expressed breastmilk, pasteurized donor human milk, infant milk formula, or re-lactation (once the mother is no longer infectious).
3) The mother can pump her breasts regularly in a hygienic manner and a healthy caregiver can feed the milk to the baby.
4) The mother should wash her hands and breasts with soap and water prior to pumping.
5) The pump and parts should be sterilized by a healthy caregiver before each pumping session.
6) The mother should wear a well-fitting mask during pumping.
7) The caregiver who will take care of the baby should be healthy and should not be a symptomatic or asymptomatic carrier of the SARS-CoV-2 virus.
8) Ideally, there should be a dedicated pump solely for the mother's use.
9) All the pump parts that have been in contact with the mother's milk and skin should be washed with soap and water after pumping. This should ideally be done by a healthy person.
10) The doctor should explain to the parents that even if the mother does not touch her baby, the baby might still get infected if another caregiver is infected with COVID-19 (symptomatic or asymptomatic infection).

Other than the aforementioned precautionary measures, the Woman Study Group of AMD issued the following suggestions after reviewing the current available data and recommendations from various health care organizations:[3]

1) If feasible, consider having someone who is well to care for and feed the expressed breastmilk to the infant in cases where the mother is too ill to breastfeed, or other situations does not allow her to do so.
2) If the COVID positive mother has evident respiratory symptoms, the mother and infant should be transiently managed separately. The expression, transportation and administration of fresh mother's milk to newborn is recommended. The Woman Study Group does not suggest pasteurization of breastmilk since it may reduce the biological and immunological value of human milk.

If the mother has a serious infection, forego breast milk expression and consider use of donated breastmilk. Additionally, the decision to use fresh mother's milk does not only depend on the mother's said COVID infection and its transmission. The compatibility of breastfeeding with the drugs that are being administered to the infected mother should be assessed on a daily, case-by-case basis.

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WHO AMONG THE PREGNANT WOMEN WITH COVID-19 INFECTION NEED ADMISSION?
STATEMENT: **Not all pregnant women with COVID-19 warrant admission. Those who are asymptomatic or with mild disease and/or stable co-morbid illness can be sent home for isolation with proper instructions and counselling. Only those with severe disease and are critically ill should be admitted.**
SUPPORTING STATEMENTS: The rationale for admission of COVID-19 pregnant women is the same with the general population and this is based on the patient's vital signs, clinical manifestation and severity of symptoms. Patients presenting with fever, cough, dyspnea and/or shortness of breath should be assessed and categorized according to the gravity of symptoms. If found to be positive for pneumonia, the management recommendation of the Philippine Clinical Practice Guidelines for Community-Acquired Pneumonia is followed.[1] The table below (Table 3-3) summarizes the classification of pregnant women with COVID-19 infection based on disease severity and provides the recommended laboratory examination and appropriate management for each category.[2,4]

Table 3-2: Disease Severity Classification of Pregnant Women with COVID-19

Disease Severity	Recommended Management
Pregnant patients with MILD SYMPTOMS AND NO CO-MORBID ILLNESS • Have no co-morbid illness • Present with mild non-specific symptoms (fever, cough, sore throat, nasal congestion, headache, muscle pain or malaise)	• No diagnostic tests are needed for this group except for RT PCR for SARS-CoV-2. • Patient may *opt to undergo home quarantine for 14 days* with strict instructions, or may stay in a community health facility. • Give symptomatic treatment and supportive care. • Most cases will not require antibiotics.
Pregnant patients with STABLE CO-MORBID ILLNESS AND MILD PNEUMONIA • Have clinical signs of **mild pneumonia** (fever, respiratory rate <30 breaths per minute, heart rate <125 beats per minute and SpO2 >92%).	• Perform RT-PCR for SARS-CoV-2, Chest X-ray with abdominal shield, complete blood count, AST, ALT and creatinine. • Patient may be managed at home or admitted in a COVID-19 designated unit and managed as **CAP-Low Risk** based on the 2016 Updated Philippine Community Acquired Pneumonia Guidelines (Appendix B1).

Disease Severity	Recommended Management
Pregnant patients with SEVERE ACUTE RESPIRATORY INFECTION (SARI) * • Present with fever, respiratory rate >30 breaths/minute, with severe respiratory distress or SpO2 <92%	• Perform the following recommended diagnostic tests: - RT-PCR for SARS-CoV-2 - Complete blood count - Comprehensive metabolic panel - Ferritin - Lactate dehydrogenase (LDH), Lactate - Procalcitonin - C-reactive Protein (CRP) - INR/PT - D-dimer - Chest X-ray with abdominal shield or CT imaging without contrast - Sputum GS/CS - Blood culture - Arterial blood gas (ABG) • Patient must be admitted and managed as a case of **CAP-Moderate Risk**. (Appendix B2)
Pregnant patients with SEPSIS OR SEPTIC SHOCK * • Present with **life-threatening organ dysfunction,** which is characterized by - Altered mental status - Difficult or fast breathing - Low oxygen saturation - Reduced urine output - Fast heart rate - Weak pulse - Low blood pressure - Cold extremities or skin mottling • *OR* laboratory evidence of coagulopathy, thrombocytopenia, acidosis and high lactate or hyperbilirubinemia ***Patients with septic shock present with persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP more than or equal to 65 mmHg and serum lactate level > 2mmol/L.*	• Perform the following recommended diagnostic tests: - RT-PCR for SARS-CoV-2 - Complete blood count - Comprehensive metabolic panel - Ferritin - Lactate dehydrogenase (LDH), Lactate - Procalcitonin - C-reactive Protein (CRP) - INR/PT - D-dimer - Chest X-ray with abdominal shield or CT imaging without contrast - Sputum GS/CS - Blood culture - Arterial blood gas (ABG) • Patient must be admitted and managed as a case of **CAP-High Risk**. (Appendix B3)

Disease Severity	Recommended Management
Pregnant patients with ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) * • Present with **new or worsening respiratory symptoms** within one week of known clinical insult • Physical exam findings include respiratory rate > 30 breath per minute and SpO2 of < 90%, with or without progressing infiltrates on CXR	• Perform the following recommended diagnostic tests: - RT-PCR for SARS-CoV-2 - Complete blood count - Comprehensive metabolic panel - Ferritin - Lactate dehydrogenase (LDH), Lactate - Procalcitonin - C-reactive Protein (CRP) - INR/PT - D-dimer - Repeat Chest X-ray with abdominal shield or CT imaging without contrast - Endotracheal tube aspirate GS/CS - Blood culture - ABG • Management is based on the **classification of ARDS** (Appendices C1-C4)

Adapted from: PSMID Interim Guidelines on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection

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HOW ARE SEVERE OR CRITICALLY ILL COVID-19 PREGNANT WOMEN MEDICALLY MANAGED?

STATEMENT:

COVID-19 pregnant patients with severe acute respiratory infection, sepsis, septic shock and ARDS should be admitted and managed in an Intensive Care Unit (ICU) setting. A multi-disciplinary team approach composed of an obstetrician, intensivist, pulmonologist, infectious disease specialist and obstetric anesthetist is recommended. In these cases, the use of anti-viral and investigational drugs for COVID-19 may be considered.

SUPPORTING STATEMENTS:

Severe respiratory symptoms from COVID-19 pneumonia are associated with a high maternal and perinatal mortality, therefore aggressive treatment is required including supportive measures with hydration and oxygen therapy. The patient should ideally be managed in a negative pressure isolation room in the ICU with the support of a multi-disciplinary team composed of obstetrician, intensivist, pulmonologist, infectious disease specialist and obstetric anesthetist.[1]

COVID-19 should be distinguished from other respiratory distress infections such as bacterial pneumonia, other viral pneumonias and non-infectious lung diseases. Appropriate broad-spectrum antibiotic should be started when there is suspected or confirmed secondary bacterial infection.[2]

Critically ill patients without shock should be treated with conservative fluid management measures.[3] Oxygen should be provided immediately to prevent hypoxemia, reduce the work of breathing and preclude respiratory failure or arrest. Oxygen saturation equal to or greater than 95% should be maintained in these patients.[4] They should be made to lie in a left lateral decubitus position for optimal uteroplacental oxygenation. Hemodialysis may be required if severe sepsis will lead to renal failure and if electrolyte imbalances become life-threatening.

Antiretroviral agents and other novel drugs for COVID-19 may be introduced in consultation with the whole multi-disciplinary team to reduce the number of deaths associated with SARS-CoV-2 infection. The healthcare team should consider the most up to date recommendations on the use of these investigational agents as their efficacy on the treatment of this emerging viral infection is yet to be proven.[2]

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WHAT ARE THE CRITERIA FOR DISCHARGING COVID-19 PREGNANT PATIENTS AND WHEN SHOULD THEY BE SCHEDULED FOR FOLLOW-UP?

STATEMENT:

The decision to discharge a pregnant patient should be individualized. Initial disease severity, resolution of clinical symptoms, need for oxygen support and supportive medications should be considered. The need to do a repeat testing or to perform additional ancillary tests would depend on the patient's exposure and clinical presentation.

SUPPORTING STATEMENTS:

The Department of Health issued a Department Memorandum No. 2020-0439 on the discharge criteria for suspect, probable and confirmed COVD-19 cases and specified that repeat testing need not be performed as a requirement for clearance. This recommendation was based on other international guidelines and recommendations and available data on the natural course of the infection, duration of virus detection, evidence of viral shedding and infectivity. This recommendation are deemed applicable to all COVID-19 patients including pregnant women.

Numerous studies on the natural course of the infection, duration of virus detection, evidence of viral shedding and infectivity were utilized as basis for recommending these guidelines. A study conducted in Italy performed RT-PCR testing in 85.9% (n=2812) and 71.5% (n=2343) of the total population at two consecutive time points less than two weeks apart. At the first time point, 73 people (2.6%) tested positive while 29 (1.2%) tested positive at the second time point. Of the confirmed positive cases, 43.2% were asymptomatic.[2] The reported rates of asymptomatic cases in other case series range from 1 to 78% and in general, asymptomatic cases are likely under-reported. The study by Arons et al. found that of the 48 patients from an aged care facility with positive PCR, 50% of patients were pre-symptomatic and 6% were permanently asymptomatic.[3]

The study by Hu et al. showed that the virus was detected for a longer period of time in those who subsequently developed symptoms (pre-symptomatic: n=5, median 12 days) compared with those who were permanently asymptomatic (n=9, median 6 days). The earliest positive RT-PCR test occurred two days before symptom onset in five pre-symptomatic cases.[4]

The duration of viral shedding around a period of infection is often considered in determining the appropriate period of isolation because it is often used as a marker of infectivity. While there is evidence of viral shedding in both asymptomatic patients and even after symptom resolution, it is unclear whether there is a correlation between the detectable viral RNA and transmissibility. A positive RT-PCR test result does not accurately indicate a replication-competent virus. An RT-PCR test

cannot distinguish between an infective virus and an inactive virus hence, the amount of viral RNA does not equate to greater infectivity.[5]

The review by Walsh did not find any study that definitively measured the duration of infectivity. However, in symptomatic patients, there is evidence of a reduction in infectivity 7–10 days after onset of symptoms.[6] Two virus culture studies obtained no infectious isolates from any sample taken eight days after symptom onset in spite of ongoing high viral loads. The study by Woelfel et al. found no infectious isolates from samples taken after the eighth day of symptom onset despite consequent high viral loads. Thus, they suggested early discharge for patients beyond day 10 of symptom onset with viral load less than 10^5 RNA copies per ml of sputum.[7] This was supported by La Scola who conducted serial RT PCR testing and viral culture on 155 patients and found that no virus could be isolated from samples collected after day eight of symptom onset despite high viral loads of 10^5 RNA copies/mL of sample.[8]

These studies support the WHO recommendation, which is to discontinue transmission-based precautions isolation included, and discharge the patient if it has been 10 days since symptom onset, and the patient has been symptom-free for at least three days. If the patient is asymptomatic, completion of 10 days isolation after first positive test should be fulfilled.[9] However, clinicians should still be careful in recommending discontinuing transmission-based precautions for all COVID-19 patients at day 10 post symptom onset even if the patient has been symptom-free for three days. Data is still limited, and conclusion in terms of the duration of infectivity is not definite. In a recent study by Yongchen et al., five asymptomatic patients had a longer median duration of virus detection (18 days) compared with five patients with severe disease (14 days) and 11 patients with non-severe, but symptomatic disease (10 days).[10] Other case series reported detection of virus in hospitalized asymptomatic adults ranging from 7 to 23 days.[11]

The Centers for Disease Control and Prevention supports using a symptom-based strategy in recommending discontinuation of isolation and transmission-based precautions. This avoids unnecessary hospital admission, isolation and exclusion from work. Isolation and precautions may be discontinued in COVID-19 confirmed patients 10 days after symptom onset, who are afebrile for at least 24 hours without the use of antipyretics, with noted improvement of other symptoms.

For asymptomatic patients, isolation and precautions may be discontinued 10 days after the first positive test results, without the need for retesting.[12] There has been evidence on the presence of replication-competent virus up to 20 days after symptoms in a limited number of patients with severe illness. While current data indicate that isolation of live virus is less likely from Day 8 after symptom onset, and most patients seroconvert by Day 15 after symptom onset, the risk of transmission

may be lower but still cannot be ruled out with the available evidence.[3] Hence, infection control experts still need to individualize decision-making, since these patients may warrant extension of their duration of isolation and precaution.

In summary, the DOH, CDC and WHO are in agreement with the following recommendations:

1) **For asymptomatic patients who test positive for SARS-CoV-2 RT PCR, isolation and other precautions can be discontinued 10 days *after the date of their first positive RT-PCR test for SARS-CoV-2 RNA.***
2) ***For COVID-19 confirmed patients with mild symptoms who have completed at least 10 days of isolation from the onset of symptoms, and has been considered clinically recovered for 72 hours* without the use of fever-reducing medications, and with improvement of other symptoms, there is no need to repeat testing prior to discharge.**
3) **For patients with moderate, severe or critical symptoms, who have completed at least 21 days of isolation in a hospital from the onset of illness, inclusive of 3 days of being clinically recovered and asymptomatic, patients may be discharged without the need for a clearance swab.**
4) **For close contacts who remain asymptomatic for at least 14 days from the last date of exposure, quarantine may be discontinued without the need for any test.**

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INVESTIGATIONAL DRUGS USED IN COVID-19

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WHAT ARE THE TREATMENT OPTIONS FOR PREGNANT AND LACTATING WOMEN INFECTED WITH COVID-19?

STATEMENT:

In general, there are no specific drugs for COVID-19. The management options for pregnant patients with COVID-19 are the same as with non-pregnant individuals, except for some considerations on the therapeutics. All of the pharmacologic treatment options being used at present are based on previous experience in treating SARS, MERS and other new influenza viruses. The drugs included in this section may be helpful in the treatment of COVID-19, but their efficacy is still under investigation and further studies are needed.

Table 4.1 Summary of Investigational Drugs Used for COVID-19 Infection

NAME OF DRUG	MECHANISM OF ACTION	EFFICACY	SAFETY	US FDA PREGNANCY CATEGORY	SAFE FOR PREGNANCY & BREAST-FEEDING	DOSAGE
Remdesivir	RNA chain terminator	Conflicting results in recent reports	No reported adverse events except for transient GI symptoms and AST elevation	Unclassified	Unknown	200mg IV on day 1, then 100mg IV OD x 10 days, infused over 30-60 minutes
Tocilizumab	Humanized monoclonal antibody	Could be an efficient treatment	Use of 6 months or more increases risk of infections and infestations	Unclassified	Unknown	4-8 mg/kg IV with recommended dose of 400 mg diluted with NSS to 100 ml, given as 2-hour infusion
Corticosteroids	Anti-inflammatory and immunomodulation	Useful in patients requiring O2 support	Causes delayed viral clearance	**Prednisolone** C **Methyl-prednisolone** C **Dexa/Beta-methasone** C	Yes	***Hydrocortisone*** 50 mg IV every 6 hours OR 100 mg IV bolus followed by infusion at 10mg/hour x 7 days

NAME OF DRUG	MECHANISM OF ACTION	EFFICACY	SAFETY	US FDA PREGNANCY CATEGORY	SAFE FOR PREGNANCY & BREAST-FEEDING	DOSAGE
Convalescent Plasma (CP)	Provision of immediate passive immunity	Has potential in reducing mortality in critically ill patients, eradication of SARS-CoV-2 RNA and improvement in clinical symptoms	Safety issues similar to blood transfusion	Not classified	Yes	Varies from 200 ml to 2400 ml in different studies
Plasmapheresis and TPE / Hemo-perfusion	Removal of inflammatory cytokines, stabilizing endothelial membranes, resetting the hypercoagulable state	Has the potential to higher extubation rates, lower mortality rates and improved laboratory and ventilatory parameters	Infection, bleeding and hematoma to needle entry site	Not classified	Yes	The total volume of plasma to be replaced was calculated as follows: plasma replacement (L) = body weight (kg) x (1/13) x (100-hematocrit)
Immuno-globulin	Blocking of macrophage Fc receptors	Few data available, more studies needed	Most reactions are mild and reversible Adjust in renal and cardiac patients	C	Yes	0.3-0.5g/kg/day x 5 consecutive days
Melatonin	Anti-inflammatory	Limited evidence shows promising results, more studies needed	Safe for short-term use High dose may increase production of pro-inflammatory cytokines	A (for short-term use)	Yes (for short-term use)	36-72 mg/day in 4 divided doses
Zinc	Mineral/essential micronutrient; inhibition of pro-inflammatory cytokines	Further studies needed	Zinc as a micronutrient is found in various multivitamin preparations. It is proven to be safe if taken in usual doses.	C	Yes	50 mg once a day

NAME OF DRUG	MECHANISM OF ACTION	EFFICACY	SAFETY	US FDA PREGNANCY CATEGORY	SAFE FOR PREGNANCY & BREAST-FEEDING	DOSAGE
Ascorbic Acid	Biosynthetic and antioxidant	Few studies show efficacy of high doses	Good safety profile	A	Yes	50 mg/kg every 6 hours x 4 days Must be given with Hydrocortisone 50 mg IV every 6 hours x 7 days
Oseltamivir	Neuraminidase inhibitor	Insufficient evidence	Well-tolerated Needs renal dose adjustment	C	Yes	***Cr Cl 30-60 mL/min***: 30 mg BID x 5 to10 days ***CrCl <30 mL/min***: 30 mg PO OD x 5-10 days ***Hemodialysis patients***: 30 mg after dialysis x 5 days
Lopinavir/ Ritonavir (LPV/RTV)	Protease inhibitor	No significant difference compared to standard treatment	Option for patients with prolonged QT interval, arrythmias, decompensated heart disease, elevated AST & ALT, G6PD deficiency or hypersensitivity to CQ & HCQ	C	Yes	200mg/50mg tab, 2 tabs BID PO x 14 days ***These drugs were withdrawn from the WHO Solidarity and the RECOVERY Trial***
Favipirarir	RNA polymerase inhibitor	More studies needed	Well tolerated but adverse events are observed in higher doses No renal dose adjustment	X	No	2400-3000 mg every 12 hours for 2 doses, then 1200-1800 mg BID PO x 5 to 7 days
Ribavirin	Inosine monophosphate dehydrogenase inhibitor RNA polymerase inhibitor	Unknown	Excessive hematologic toxicity	X	No	1.2-2.4 grams PO every 8 hours

NAME OF DRUG	MECHANISM OF ACTION	EFFICACY	SAFETY	US FDA PREGNANCY CATEGORY	SAFE FOR PREGNANCY & BREAST-FEEDING	DOSAGE
Interferon	Biologic response modifier/ cytokine	With potential role especially at the late stage of the disease Used together with LPV/RTV	Fever, headache and fatigue are common at initial injection Neuropsychiatric side effects can be most troublesome	C	Unknown	5 million units BID given in 2ml of sterile water administered by nebulization
Azithromycin	Bacteriostatic Immuno-modulatory or anti-inflammatory effects in some in vitro and animal research	Addition of this drug to other regimens does not improve outcomes	Good safety profile Precautions for those with cardiac, liver, and renal disease, and myasthenia gravis	B	Yes	500mg OD on day 1, then 250 mg OD PO x 4 days
Chloroquine (CQ) & Hydroxy-chloroquine (HCQ)	Immuno-modulatory	Lack of efficacy reported in studies	Latest evidence point out to increased morbidity and mortality associated with these anti-malarial drugs	C	Yes	***Both of these drugs were withdrawn from the WHO Solidarity Trial***

Below are the detailed information (i.e. mechanism of action, efficacy, safety, pregnancy category, breastfeeding safety and dosage) on the various investigational drugs used for COVID-19.

I. REMDESIVIR

Remdesivir, or GS-5734, is a monophosphoramidate prodrug of an adenosine analog. This investigational drug was developed by Gilead Sciences, Inc. intended to treat Ebola virus. In its active form, this nucleotide analog can block nucleotide synthesis and stop viral replication. The mechanism of action of remdesivir is thru binding to the RNA-dependent RNA polymerase and acts as an RNA chain terminator.[1]

Remdesivir has broad spectrum antiviral and was found to be effective against human and pre-epidemic zoonotic coronaviruses (CoVs) and can inhibit replication of SARS-CoV and MERS-CoV in vitro. [2] Animal experiments showed that remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS- CoV, improve lung function, and alleviate pathological damage to lung tissue. [3] Similarly,

remdesivir potently blocks SARS-CoV-2 infection at low micromolar concentrations and has a high selectivity index. [3,4,5]

Drug Interactions: Clarithromycin, Rifampin, Phenytoin, Phenobarbital, St. John's Wort

Pregnancy Category: Unclassified

EFFICACY OF REMDESIVIR IN TREATMENT OF COVID-19

There is conflicting data based on the efficacy of remdesivir as a treatment for COVID-19 infection based on latest clinical trials.

Remdesivir was included as one of the four drugs investigated in the Solidarity trial. This international trial was launched by the WHO, and is considered the largest international randomized trial for COVID-19 treatments, having enrolled 12,000 patients in 500 hospitals from 30 countries.

In the interim results of the WHO Solidarity trial released last October 15, 2020, it was found that **remdesivir has little or no effect on the overall mortality, initiation of ventilation and duration of hospital stay in admitted COVID-19 patients**. The study results are still subject to peer-review as of writing.[9]

The Adaptive COVID-19 Treatment Trial (ACTT-1) also evaluated remdesivir as therapeutic agent for COVID-19. This study is an multicenter, adaptive, randomized, double-blind, placebo-controlled trial conducted in several countries and hospital sites globally. A total of 1062 patients were included (541 assigned to remdesivir group and 521 assigned to the placebo or control group). The final report of the study showed shorter median recovery time of 10 days (95% CI, 9 to 11) in the remdesivir group, compared to the placebo group with 15 days (95% CI, 13 to 18). They also found that patients who received remdesivir were found to be more likely to have clinical improvement on day 15. Mortality rates at day 15 and day 29 were likewise lower for the remdesivir group (6.7% and 11.4% respectively) vs. placebo (11.9% and 15.2% respectively). Based on this trial, **remdesivir is superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.**[10]

Despite the conflict in recent trial results, the US FDA has approved the use of remdesivir in adult and pediatric patients 12 years old and above and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization.[11]

SAFETY ISSUES ON THE USE OF REMDESIVIR

There are reported transient gastrointestinal side effects and aminotransferase elevation with remdesivir use.

"Among the first 12 patients confirmed by the CDC to have COVID-19 in the United States, 3 were treated with remdesivir via compassionate use protocol. All patients reported transient gastrointestinal symptoms and aminotransferase elevation. All patients are reportedly recovering, but the authors were unable to assess the efficacy or safety of remdesivir based on the lack of comparator and confounding treatments, including concomitant use in steroids in one patient." There were no adverse events to remdesivir reported for the COVID-19 patient treated in the US last January 2020.[1]

Remdesivir has been used for compassionate use in 2015 for a case of late relapse with CNS involvement in a patient who was previously treated for severe Ebola virus infection. The patient was a 39-year old female nurse from Scotland, who acquired the Ebola infection after a humanitarian mission in Sierra Leone. She was treated with remdesivir for her relapse, as studies have shown that the antiviral drug can cross the blood-brain barrier. The patient had improvement of symptoms and there were no reported adverse events in the case, apart from a minimal rise in the patient's serum amylase levels. [7]

SAFETY OF REMDESIVIR USE IN PREGNANCY

There is currently no data available on the use of remdesivir among pregnant patients.

In preclinical trials, studies showed remdesivir is considered non-genotoxic. In the reproductive and development toxicity studies, the only notable finding was a decrease in corpora lutea, a consequent decrease in implantation sites and viable embryos, and lower ovary and uterus/cervix/oviduct weights in the rat fertility study; these changes were observed at a systemically toxic dose. There were no remarkable findings in male rats in the fertility study, no adverse findings in the developmental toxicity studies in rats and rabbits, and no adverse changes in the pre- and postnatal study in rats.[8]

SAFETY OF REMDESIVIR USE IN BREASTFEEDING

There is currently no data available on the use of remdesivir among lactating women.

DOSAGE OF REMDESIVIR FOR TREATMENT OF COVID-19 INFECTION

Remdesivir is given at 200 mg IV on day 1, followed by 100 mg IV daily up to 10 days and is infused over 30-60 minutes.[1,3]

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II. TOCILIZUMAB

Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 receptor approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.[3] Tocilizumab has been shown to be effective against cytokine release syndrome resulting from CAR-T cell infusion against B cell acute lymphoblastic leukemia.[2] US FDA pregnancy category for tocilizumab is not assigned due to limited data, so it should be used during pregnancy only if the benefit outweighs the risk.[8]

EFFICACY OF TOCILIZUMAB IN THE TREATMENT OF COVID-19

Tocilizumab is a promising drug in the management of COVID-19. More research is needed to prove its efficacy in treating patients with coronavirus infection.

A case series of 14 COVID-19 cases showed that T cells are reduced significantly in COVID-19 patients, and the surviving T cells appear functionally exhausted. T cell numbers are negatively correlated to serum IL-6, IL-10 and TNF-α concentration.[2]

In the pathogenesis of SARS, a cytokine storm occurred, involving a considerable release of proinflammatory cytokine including IL-6, tumor necrosis factor-α (TNF-α) and IL-2. Similar to the changes in SARS and MERS-CoV, in COVID-19, higher plasma levels of cytokines including IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF) interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A) and TNF-α were found in ICU patients, which implies that a cytokine storm occurred.[9]

Interleukin-6 (IL-6) plays a central role in cytokine storm. The classical IL-6 signal is limited to the cells that express IL-6R and plays a leading role in the low level of IL-6. The binding of tocilizumab with cell-related IL-6R and soluble IL-6R can inhibit classical and trans signal. Therefore, tocilizumab can inhibit cytokine release syndrome.[10]

In a study of 21 patients who were treated with tocilizumab 400 mg once through an IV drip added on top of standard care, results showed that patients improved immediately after the treatment. Clinical symptoms of all patients improved remarkably with good prognosis after the treatment. This suggests that tocilizumab could be an efficient therapeutic for the treatment of COVID-19, by blocking of IL-6-associated febrile and inflammatory storm response.[9] A case study of a 40-year old man with COVID-19 interstitial pneumonia treated with a combination of anti-

interleukin 6 (IL-6) agent (tocilizumab) and hemoadsorption showed that the combination of tocilizumab and hemoadsorption could be valuable in the treatment of COVID-19-associated pneumonia and ARDS that are caused by the release of inflammatory mediators.[11]

A systematic review of three (3) indirect pre-clinical studies and 28 clinical studies including 5776 patients with COVID-19 (13 with a comparison group, 15 single-arm) concluded that the evidence on tocilizumab's efficacy and safety does not suffice to issue recommendations regarding its use for COVID-19.[12]

SAFETY ISSUES ON THE USE OF TOCILIZUMAB

More studies are needed to elucidate the adverse events associated with use of Tocilizumab.

Among patients with rheumatoid arthritis who received tocilizumab over a period of at least 6 months, the most common adverse events include infections and infestations.[5] Other common adverse events by system organ classes include abnormal laboratory findings (investigations), musculoskeletal and connective tissue disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders and blood and lymphatic system disorders.[3] Tocilizumab can cause hypertension, diabetes and other cardiovascular disease.[10] Long term studies are essential to determine safety of tocilizumab over time.

SAFETY OF TOCILIZUMAB DURING PREGNANCY

Few initial studies demonstrated no increase in abortion or incidence of congenital anomalies among women and fetuses exposed to this drug during pregnancy. More studies are needed to prove the safety of use in pregnancy.

Women found to have been exposed to tocilizumab shortly before or during pregnancy under the Roche Global Safety Database[4] and the Chugai's tocilizumab safety database[6] indicated no increased rates of spontaneous abortion or congenital abnormalities. No increased risk for adverse pregnancy outcomes were observed after paternal exposure in pregnancies with known outcome.[4] Considering the limitations of global safety databases, the data do not yet prove safety. Further study is necessary to confirm the benefit-risk profile of tocilizumab treatment during pregnancy.[5]

SAFETY OF TOCILIZUMAB DURING BREASTFEEDING

More studies are needed to prove the safety of use of Tocilizumab among lactating women.

A study measured tocilizumab concentrations in the breastmilk of two nursing mothers with rheumatoid arthritis and evaluated the safety of their breastfed infants. Tocilizumab concentrations in breastmilk were measured frequently after injections, reaching a peak 3 days after each injection and decreasing gradually thereafter. The maximum tocilizumab concentrations in breast milk was 148.2 ng/ml after 3 days. Breastmilk levels of tocilizumab ranged from 1/500 to 1/1000 of those in serum. Infants exclusively breastfed experienced no serious infections that required hospitalization and no developmental delays.[7] Further studies are needed to show impact of tocilizumab exposure on breastfeeding infant.

DOSAGE OF TOCILIZUMAB FOR THE TREATMENT OF COVID-19

Tocilizumab is administered at an initial dose of 4-8 mg/kg, prepared as 400 mg diluted with 0.9% normal saline to 100 mL, given as a 2-hour infusion. A single extra dose may be given after 12 hours if the initial medication is not effective.

Tocilizumab can be given to patients in severe conditions with extensive lung lesions and increased level of IL-6 in laboratory testing.

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III. CORTICOSTEROIDS

Many of the clinical use of corticosteroids have been associated to their potent anti-inflammatory and immune-modulating properties.[1] The corticosteroids are steroid hormones produced by the adrenal cortex, consisting of 2 major physiologic and pharmacologic groups: (1) glucocorticoids, which have important effects on carbohydrate metabolism, catabolism, immune responses, and inflammation; and (2) mineralocorticoids, on the other hand has pronounced effects on fluid and electrolyte balance.[2] Corticosteroids encompass a spectrum of exclusively glucocorticoid effects to exclusively mineralocorticoid effects, thus, steroid compounds are selected based on their appropriateness for a given treatment.[1]

The anti-inflammatory property is mainly attributed to their inhibitory effects on the action of enzyme essential to the production of inflammatory compounds, the phospholipase A2. Its physiologic effects are the result of several biochemical pathways. One of these pathways is through their production of proteins called lipocortins. This inhibits the production of multiple inflammatory cells (macrophages, monocytes, endothelial cells, basophils, fibroblasts and lymphocytes) that are crucial in generating an inflammatory response. Thus, it effectively halts the inflammatory cascade. Furthermore, they are also recognized for its immunosuppressive property. This may be associated to the suppression of lymphocyte function and multiplication, altering the immune response.[1,2]

Drug Interactions: Corticosteroids can interact with drugs that affect the levels of potassium in the blood (e.g. diuretics, certain laxatives); drugs that have known side effects when potassium levels drop in the blood stream (e.g. digitalis); drugs resulting in decreased cortisone in the blood (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, primidone) or decrease the gastrointestinal absorption of cortisone (e.g. gastric dressing); and lithium (corticosteroids decrease blood levels of lithium). Moreover, corticosteroids can increase blood sugar level and blood pressure.

Pregnancy Category: Prednisolone – C
Methylprednisolone – C
Dexamethasone and Betamethasone – C

EFFICACY OF CORTICOSTEROIDS IN THE TREATMENT OF COVID-19

Systemic corticosteroid therapy (either oral or intravenous dexamethasone 6mg/day or intravenous hydrocortisone 50mg every 8 hours) is recommended ONLY for COVID-19 patients requiring oxygen support (severe and critical) in a relatively short course of up to 7 to 10 days.

The preliminary report of the Randomised Evaluation of COVID-19 therapy (RECOVERY Trial) done to investigate an array of potential COVID-19 treatments including dexamethasone at a lowest possible effective dose was released. Results gathered from 2,104 patients randomized to receive dexamethasone 6 mg (orally or intravenously) once a day for 7 to 10 days were compared to 4,321 patients randomized to receive usual care alone, showed that judicious use of dexamethasone significantly reduce 28-day mortality by one-third among patients requiring mechanical ventilation(29.0% vs 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001) and nearly one-fifth in patients on oxygen support apart from mechanical ventilation(21.5% vs 25%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002). However, dexamethasone did not offer benefit in patients not requiring respiratory support (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). Recorded death within 28 days were 454 patients under the dexamethasone arm and 1,065 patients under the usual care arm.[1]

Thus, the group concludes that corticosteroids, particularly dexamethasone has shown to improve patients requiring oxygen support who has more serious condition and has shown no benefit among asymptomatic and mild cases. Hence, dexamethasone is only reserved for use in the severely ill and critical patients.

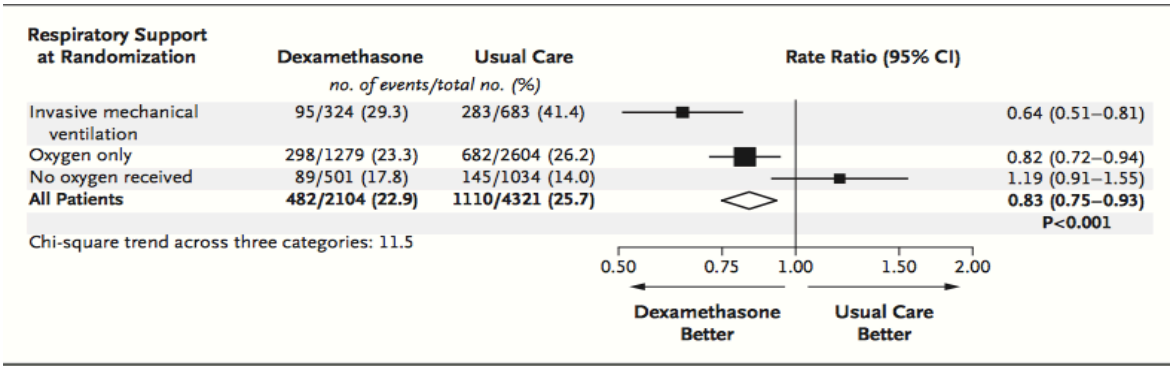

Figure 4.1 Effect of dexamethasone on 28-day mortality, according to respiratory support at randomization[1]

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence interval

Note:
Corticosteroid equivalence in terms of glucocorticoid effect
Dexamethasone 6mg once daily
Hydrocortisone 150mg (50mg every 8 hours)
Prednisone 40mg daily
Methylprednisolone 32 mg (8mg every 6 hours or 16mg every 12 hours)

Intravenous and oral systemic corticosteroids are similar in terms of bioavailability. Thus, route of administration may be tailored to patients' status and needs without apprehensions on reduced drug absorption.[2]

SAFETY ISSUES ON THE USE OF CORTICOSTEROIDS

Corticosteroids are known to have various side effects. Benefits and risks should always be weighed.

The following harmful side-effects of corticosteroids are mostly associated with the pattern of linear increase of dose and duration of therapy.

1. DELAYED VIRAL CLEARANCE: This may be associated with the alterations in the immune system primarily by the T-cell mediated responses by the corticosteroids leading to immunosuppression.[11]

2. PSYCHOSIS: Adverse effects occur in up to 90% of patients taking even at a low glucocorticoid dose (≤7.5mg/dL) with a duration of >60 days. This may be related to the disturbance of the cortisol pathway by the synthetic steroids stimulating the glucocorticoid receptors, which has synthetic steroid preference, suppressing the adrenals cortisol production, promoting an imbalance of glucocorticoid versus mineralocorticoid receptor stimulation, leading to cognitive-emotional disturbances. However, prognosis is favorable once the medication is reduced or discontinued.[11]

3. DIABETES: Glucocorticoids decrease the liver's sensitivity to insulin, thereby increasing hepatic glucose output. Screening guidelines such as fasting glucose ≥126 mg/dL or HbA1c ≥6.5% should be done to diagnose steroid-induced diabetes and repeated for confirmation as recommended by American Diabetes Association guidelines. Management is similar to that of type 2 diabetes mellitus. Patients with pre-existing diabetes, blood sugars should be measured more often than in patients without preexisting diabetes, and medications should be adjusted to maintain adequate control.[18]

4. OSTEOPOROSIS: Bone mineralization is altered with glucocorticoid use through inhibiting gastrointestinal calcium absorption and shifting signaling-molecule production to favor bone resorption. It is also associated with the reduction of the replication, differentiation and function of osteoblasts and increasing the rate of mature cells apoptosis, thereby depleting the osteoblastic cell population and inhibiting the function of mature cells. Prevention of osteopenia by calcium with vitamin D when using glucocorticoid doses ≥5 mg/day and starting bisphosphonates is indicated after densitometry evaluation.[19]

5. AVASCULAR NECROSIS/ OSTEONECROSIS: A combined effect of high dose-duration-response relationship of corticosteroids, underlying disease and host susceptibility causes corticosteroid-induced avascular necrosis. This condition could be secondary to increased osteocyte apoptotic rate due to glucocorticoids

resulting in diminution of bone hydraulic support and disruption of normal bone vascularity. A high corticosteroid dose of >2g/day corticosteroid (prednisone equivalent), each 10mg/day increase was associated with 3.6% increase in osteonecrosis rate especially in the first 3 months, is associated with a higher risk of developing osteonecrosis.[19]

6. SECONDARY FUNGAL INFECTION: SARS infection experience showed induced mild immunosuppression and further immunosuppression could be aggravated following a high-dose and prolonged corticosteroid use. Hence, use of corticosteroid in the treatment of SARS is discouraged.[20]

SAFETY OF CORTICOSTEROIDS IN PREGNANCY

There is limited data to support the use of corticosteroids for the treatment of COVID-19 infection in pregnant women. However, corticosteroid use can be considered with prudence in conditions where its clinical benefits outweigh its risks for both the mother and the fetus.

Physiological adaptive changes during pregnancy particularly the pregnancy-induced immunological changes leaves women in a state of immunosuppression, predisposing these women to infections including COVID-19 infection over the general population.

Corticosteroids, known for promoting immunosuppression through reduction of lymphocyte proliferation and function, thereby suppressing mainly the cell-mediated immunity and of lesser degree the humoral immunity[11] especially among pregnant women. Together with the limited studies available concerning the use of corticosteroid for COVID-19 pregnant women, data suggests that there is inadequate evidence to recommend the use of corticosteroids for pregnant COVID-19 patients.[21]

Corticosteroids are classified C under FDA category, translated as animal studies revealed adverse effects on the fetus and there are no controlled studies in women and animals available. Thus, these should be given with discretion if potential benefits outweigh potential risks to the fetus.[22]

In a systematic review investigating adverse pregnancy and birth outcomes following corticosteroid exposure, results showed that there may be a small increased risk of cleft lip with or without cleft palate with use of corticosteroid at first trimester of pregnancy by 3/1000 births. However, there is insufficient evidence to support an increased risk of preterm birth, low birth weight or preeclampsia after corticoid use in pregnancy. They also suggested that use of prednisone dose at less than 20mg/day in pregnancy is generally safe, however higher doses are considered

in cases of more advanced disease. Inflammation from uncontrolled autoimmune activity (Rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease) is potentially more harmful to maternal and fetal health than high-dose steroids.[23]

However, WHO recommends use of antenatal corticosteroid only in situations where no clinical evidence of maternal infection is observed, and adequate childbirth and newborn care is accessible. The clinical benefits of its use must outweigh the risks of potential harm to the mother and the preterm newborn, hence thorough discussion with the woman regarding its risks and benefits is highly encouraged.[3]

The most commonly used corticosteroid in pregnancy are prednisolone/prednisone, dexamethasone and betamethasone. Betamethasone and Dexamethasone are synthetic corticosteroids which has the ability to cross the placental barrier. These are recommended treatment for anticipated preterm birth. Betamethasone is administered 12mg intramuscularly daily x 2 doses and Dexamethasone 6mg intramuscularly every 12 hours x 4 doses. But among these three, prednisolone is the most commonly used in medical conditions, predominantly for purposes of immunosuppression and autoimmune treatments other than anticipated preterm labor in pregnancy.[24]

SAFETY OF CORTICOSTEROIDS IN BREASTFEEDING

Available data suggests that maternal corticosteroid (prednisone, prednisolone, betamethasone) use during lactation has no documented adverse effect on breastfed infants.

Generally, the amount of prednisone measured in breastmilk are very low. No adverse effects were reported in breastfed infants with maternal use of any corticosteroid during breastfeeding. Those requiring high maternal doses (especially with use of prednisolone instead of prednisone) warrants avoidance of breastfeeding for 4 hours. High doses might occasionally cause temporary loss of milk supply.[28]

DOSAGE OF CORTICOSTEROIDS IN THE TREATMENT OF COVID-19

The recommended dose is 50 mg IV every 6 hours, or 100 mg IV bolus followed by an infusion of 10 mg/hour for seven days.[29]

Low dose hydrocortisone should be added to the treatment regimen for patients with septic shock that is unresponsive to IV fluids and vasopressor therapy.

DOSAGE OF CORTICOSTEROIDS IN ANTENATAL CORTICOSTEROID THERAPY AND COVID-19 TREATMENT

Pregnant patient in preterm labor with concomitant COVID-19 infection warrants antenatal dexamethasone for fetal lung maturity (Dexamethasone 6mg every 12 hours for 4 doses) then continue dexamethasone dose for maternal COVID-19 infection treatment (Dexamethasone 6mg orally or intravenously daily for 7-10 days). [31]

WHO maintains its recommendation in giving antenatal steroids for pregnant women at risk of preterm birth from 24 to 34 weeks age of gestation, provided there are no signs of maternal infection. Dexamethasone has proven its efficacy at its present high dose but with short duration and has been considered standard of care for pregnancies at risk of preterm birth. Betamethasone and dexamethasone are the only two corticosteroids recommended for fetal lung maturity owing to its evidence of adequate to high levels of placental transfer with noted low rates of mineralocorticoid effect. However, in pregnancy, prolonged and repetitive use of these corticosteroids for fetal lung maturity may cause adverse effects such as adverse neurologic outcomes, small head circumference, fetal growth restriction and increased chances of neonatal hypoglycemia. Hence, replacement of dexamethasone with an agent that has limited placental transfer should be used.

Methylprednisolone together with prednisone, prednisolone and hydrocortisone are known to be metabolized by placental 11-b-hydroxylase steroid dehydrogenase-2, limiting its placental transfer. In a meta-analysis of randomized controlled trials done to investigate the effects of corticosteroids using a low dose methylprednisolone among 966 patients with acute lung injury, acute respiratory distress syndrome and severe pneumonia, the review showed a reduction in the mortality rate and faster improvement in patients requiring mechanical ventilation with the use of low dose methylprednisolone.[15] In a comparative study done to assess pharmacokinetic properties of methylprednisolone and prednisolone concentration in the bronchoalveolar lavage of adult rabbits, results showed higher lung tissue penetration and longer lung residence time in the methylprednisolone group.[16]

Thus, amongst the mentioned glucocorticoids, methylprednisolone is notably the ideal agent for the continuity of COVID-19 treatment in pregnant women. Furthermore, glucocorticoids' favorable effect on severe viral infections as observed in the RECOVERY Trial is likely dependent on the choice of appropriate dose, time/duration, and patient. High doses may be more harmful than helpful. Hence, drug administration must be started and observed at the lowest effective dose with the shortest duration possible, given at a time when control of viral replication is paramount and inflammation is minimal.[1,14,17]

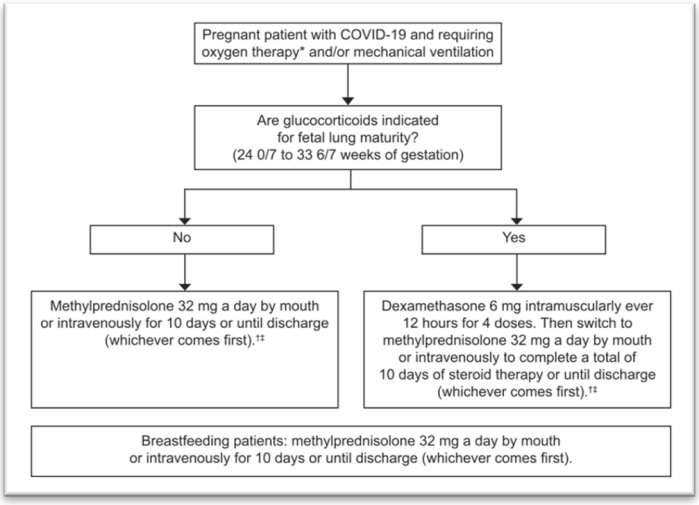

Figure 4.2 Use of steroids for pregnant or breastfeeding patients with COVID-19.[14]

*Initiated when SpO2 values fall below 94%.
+Alternative regimens: prednisolone 40mg administered by mouth or IV hydrocortisone 80mg twice daily.
±Owing to risk of hyperglycemia, close glucose monitoring is indicated with possible insulin administration.

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IV. CONVALESCENT PLASMA (CP)

Convalescent Plasma (CP) is taken from recovered COVID-19 patients. It contains antibodies against SARS-CoV-2 that provide passive immunity until the patient can develop an active immune response. The passive immunity is provided through neutralizing antibodies or possibly through other immune mediators directed against SARS-CoV-2. This mode of therapy has been used to provide immediate immunity to susceptible individuals against pandemic viruses such as SARS, MERS, Influenza A(H1N1) and Ebola.

Mode of Action: The efficacy of CP in providing immediate immunity is associated with the concentration of neutralizing antibodies (Nabs) in plasma from recovered donors. In SARS-CoV and MERS, Nabs bind to spike1-receptor binding protein (S1-RBD), S1-N-terminal domain and S2, thus inhibiting the entry and limiting viral amplification.

Drug Interactions: None

Pregnancy category: Not classified, but if benefits will outweigh the risks, may use in pregnancy

EFFICACY OF CONVALESCENT PLASMA IN THE TREATMENT OF COVID-19

Available data on the efficacy of CP showed conflicting results.

In an open-label RCT of Li L et al. conducted in Wuhan, China, involving 103 patients with severe or life-threatening COVID-19, comparing CP therapy + standard treatment vs standard treatment alone, did not result in statistically significant improvement in time to clinical improvement (52% vs 43%, HR for improvement 1.4, 95% CI 0.79-2.49) and mortality (16% vs 24%, OR 0.65, 95% CI 0.29-1.46) within 28 days. However, this trial was terminated early due to poor enrollment. In a subset analysis of this RCT, patients who have severe but not life-threatening disease and received CP have greater rate of clinical improvement (91% vs 68%, HR 2.15, 95% CI 1.07-4.32). There was also note of improved nasopharyngeal viral RNA clearance at 72 hours compared with standard treatment alone (87% vs 38%).[1]

A Cochrane review which included an RCT and 3 non-randomized studies, results showed no significant differences in all-cause mortality, time to death and improvement of clinical symptoms.[2]

The a systematic review of Rajendran et al. that included 5 studies (27 patients), showed the following findings: a) CP may reduce mortality in critically ill patients, b) increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was

observed in almost all the patients after CP therapy, and c) Beneficial effect on clinical symptoms after administration of CP. However, due to heterogeneity of these studies, no meta-analysis was performed.[3]

SAFETY ISSUES IN THE USE OF CONVALESCENT PLASMA

Safety issues of convalescent plasma use are similar to blood transfusion.

Since CP is a blood component, safety issues are similar to blood transfusion, such as allergic reactions, infections such as HIV and Hepatitis B & C. These risks are very low. US FDA authorized CP therapy for people with COVID-19. The risk of getting COVID-19 from CP has not been tested yet. But researchers believe that the risk is low because donors have fully recovered from infection.

SAFETY OF CONVALESCENT PLASMA IN PREGNANCY AND BREASTFEEDING

Pregnancy and breastfeeding are not contraindications to blood component transfusion.

DOSAGE OF CONVALESCENT PLASMA IN THE TREATMENT OF COVID-19

The doses of CP therapy used in different studies is varied.

A Chinese pilot study showed a single use of 200 ml CP with neutralizing antibody titers >1:640. Another study by Zhang et al. reported a maximum of 2400 ml of CP.[4]

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V. PLASMAPHERESIS AND THERAPEUTIC PLASMA EXCHANGE (TPE)/HEMOPERFUSION

Plasmapheresis is a method of separating and removing the plasma component, usually less than 15% of the patient's blood volume and therefore does not require replacement of the removed plasma. TPE is when plasmapheresis is followed by replacement with fresh frozen plasma (FFP) infusion. In TPE large volume is removed from the patient. TPE may play a role in the therapeutic strategy in patients with sepsis with multiple organ failure, thrombotic microangiopathies, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, DIC, catastrophic antiphospholipid syndrome, vasculitides, SLE, liver failure, etc.[1]

Mode of action: Removal of inflammatory cytokines, stabilizing endothelial membranes, and resetting the hypercoagulable state.

Drug interactions: None

Pregnancy category: Not classified, but if benefits will outweigh the risks, may use in pregnancy

EFFICACY OF TPE IN THE TREATMENT OF COVID-19

Currently, there are no published trials on the effectiveness and safety of TPE as an adjunctive treatment for severe COVID-19.

In a case series of critically ill adult men and non-pregnant women (31 patients) with laboratory-confirmed COVID-19 in Oman, the group that received TPE was associated with higher extubation rates than the non-TPE group (73% vs 20%, p=0.018). They also have lower mortality rates at 14 and 28 days post TPE (0 vs 35%, p = 0.0333). However, all-cause mortality was only marginally lower in the TPE group compared to non-TPE group (9.1% vs 45%, p= 0.055, power = 66%). Laboratory and ventilatory parameters also improved post TPE (n =11).[2]

SAFETY ISSUES IN THE USE OF TPE

Plasmapheresis is a safe procedure when performed by experienced personnel. The most frequent adverse event is infection of the venous access site. Others are bleeding or hematoma from needle placement.

SAFETY OF TPE IN PREGNANCY AND BREASTFEEDING

TPE has been successfully and safely used in the treatment of pregnancy complicated by thrombotic thrombocytopenic purpura or persistent postpartum microangiopathic hemolytic disorders.

A low risk of morbidity and fatalities associated with TPE has been reported, but the incidence of these complications does not seem to be affected by pregnancy.[3] No data on the safety of TPE on breastfeeding.

DOSAGE OF TPE IN THE TREATMENT OF COVID-19

Optimum numbers of TPE is not yet established at this time.

In a case series of 31 COVID-19 patients in Oman, 11 had TPE as a mode of treatment. TPE was given after 7 and up to 14 days of illness. The total volume of plasma to be replaced was calculated as follows: plasma replacement (L) = body weight (kg) x (1/13) x (100-hematocrit). TPE was performed through a standard femoral central venous catheter (Fr 12). Each patient underwent a total of 5 procedures.[2]

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VI. INTRAVENOUS IMMMUNOGLOBULIN

It was in 1952 that immune globulin products were used in the therapy of primary immune deficiency states.[1] Intravenous immunoglobulin, or IVIG preparations contain pooled immunoglobulin G (IgG) from the plasma of about a thousand blood donors. These intravenous preparations contain >95% unmodified IgG with trace quantities of immunoglobulin A (IgA), or immunoglobulin M (IgM). Sorbitol-based formulae are now utilized for intravenous (IV) administration as compared to previous sucrose-based preparations, which are given intramuscularly, the IV route decreases adverse reactions.[2]

The primary mode of action is blocking of macrophage Fc receptors among patients with idiopathic thrombocytopenic purpura (ITP) and other autoantibody-related cytopenias. Among those with Kawasaki condition, and dermatomyositis, IVIG inhibits production of membrane attack complexes and complement-mediated tissue damage by binding activated components and so preventing deposition on certain tissues.[3] Some studies have also shown that IVIG results in a kinetic depression of complement (C_3) uptake and modifies process of complement fragment deposition on erythrocytes. Aside from this, IVIG also has natural antibodies. IgG, IgM, and IgA antibodies are important components of IVIG preparations that are immunoregulatory. These natural antibodies bind to pathogens, may remove senescent molecules, cells, and tumors, may induce remyelination, and inhibit growth of autoreactive B-cell clones.[4]

Clinical utility of IVIG preparations is in the therapy of many autoimmune, infectious, and idiopathic conditions. They are approved for treatment of motor neuropathy, chronic lymphocytic lymphoma, demyelinating polyneuropathy, Kawasaki disease, and ITP. A wide range of inflammatory and autoimmune diseases have benefited from intravenous administration of IVIG, and these conditions range from skin disorders to transplant rejection, and neurologic conditions. They also have been used in treating persons afflicted with Guillain-Barre syndrome (GBS), multiple myeloma, myasthenia gravis, factor VII syndrome, autoimmune neutropenia, post-transfusion purpura, and polymyositis/dermatomyositis.[5]

US Food and Drug Administration has approved indications for IVIG:

a. Chronic lymphocytic leukemia
b. Common variable immunodeficiency
c. Chronic inflammatory demyelinating polyneuropathy
d. Primary immunodeficiency disorders with defects in humoral immunity
e. Immune-mediated thrombocytopenia
f. Kawasaki disease
g. Chronic B-cell lymphocytic leukemia
h. Pediatric HIV type I infection
i. Multifocal motor neuropathy

Additional data on the uses of IVIG include the following:

a. In obstetrics – may be helpful in treating recurrent pregnancy loss
b. Monoclonal gammopathy-associated systemic capillary-leak syndrome (Clarkson disease) – possible survival benefit if IVIG is used for prevention[6]
c. Miller Fisher syndrome – no effect on treatment[7]
d. Pyoderma gangrenosum – effective as sole immunomodulatory agent for cases unresponsive to steroids[8]
e. Peripheral polyneuropathy in Churg-Strauss syndrome – may have benefit[9]

Drug Interactions: IVIG preparations may interact with

a. Selected live viral vaccines such as measles, mumps, and rubella-containing vaccines, yellow fever vaccine – may decrease efficacy of live vaccines (may delay giving the IVIG if a live vaccine is administered the previous month, or may repeat the dose of the live vaccine after completing IVIG therapy)[10]
b. Estrogens – when given concomitantly, there may be increased risk of thromboembolic episodes[11]
c. Nephrotoxic agents – when given together may increase risk of renal failure[12]

Pregnancy Category: US FDA Category C

Whole immune globulins have been known to cross the placenta increasingly after the 30th week age of gestation. But clinical experience does not show ill effects during pregnancy and on the unborn fetus. If given before delivery among gravidas with ITP, the platelet response and clinical effects were the same in the mother and the baby. From this knowledge, there may be potential benefits, which may warrant use of this drug during pregnancy after weighing risks and benefits.[13]

EFFICACY OF IMMUNOGLOBULIN IN THE TREATMENT OF COVID-19

Few data are associated with the efficacy of IVIG in the therapy of COVID-19. More studies are needed.

The Immunology and Allergy Clinical Reference Group of the NHS England, does not recommend use of IVIG in treating patients with coronavirus infection. The literature currently does not provide much rationale for use of this drug in the therapy of COVID-19 infection. IVIG does not contain the appropriate antibodies against SARS-CoV-2.[14]

On one hand, a study was published recently regarding use of IVIG for deteriorating patients with COVID-19 infection in China. In this practice, IVIG was used in three critical patients diagnosed with SARS-CoV-2 infection. The drug is infused at a high dose regimen of 0.3-0.5 g/kg/day or about 25g/day x 5 days to the 3 patients who were all diagnosed with severe COVID-19 infection. In this review, all the

patients improved significantly after administration. The authors based the utility of this drug on experience with therapy of neuromuscular disorders, thrombocytopenic purpura and other immune diseases, as an immune modulator. There were no reported side effects among these patients. All 3 had return to normal body temperature in one to two days, and were relieved of respiratory depression in 3-5 days of therapy. The authors concluded that high dose IVIG therapy might be a promising treatment option for early stage of clinical deterioration among patients suffering from this condition.[15]

A current study is ongoing as of writing of this document and it is entitled "A Randomized, Open-label, Controlled, Single-center Study to Evaluate the Efficacy of Intravenous Immunoglobulin Therapy in Patients With Severe 2019-nCoV Pneumonia", which includes 80 patients who are randomized to standard of care or to IVIG for severe coronavirus pneumonia. Patients are randomized to IVIG therapy at 0.5g/kg/day for 5 days plus standard of care and to placebo which is standard of care only. Outcome measures include clinical improvement, decrease in lung injury, 28-day mortality, duration of mechanical ventilation, duration of hospitalization, proportion of patients with negative RT-PCR results, and occurrence of adverse events. The study started last February 10, 2020 and will finish by June 30, 2020. We are awaiting the results with regard to safety and efficacy of IVIG in the therapy of severe COVID-19 pneumonia.[16]

From the Clinical Practice Guidelines (CPG) for COVID-19 formulated by the Philippine Society for Microbiology and Infectious Diseases (PSMID), there was no mention of IVIG as an investigational drug.

Recommendation Number 8 from the PSMID-PCCP-PCP-PRA-PCHTM Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection, states that there is insufficient evidence to support the use of IVIG for the management of COVID-19 among severe hospitalized patients except in the context of a clinical trial.[26]

SAFETY ISSUES IN THE USE OF IMMUNOGLOBULIN

Side effects have been known to occur in 5-15% of patients receiving IVIG therapy.

Most reactions to IVIG therapy are mild and reversible. After an intravenous infusion, patients may have flushing, headache, chills, myalgia, tachycardia, wheezing, back pain, nausea, and hypotension. If any of these occurs during the infusion, the rate should be slowed or discontinued. Pre-medication may be done with antihistamines, or hydrocortisone.

The following are potential adverse effects of IVIG:

a. In IgA deficiency states, serious anaphylactoid reactions may occur and this can be prevented by using IgA-depleted IVIG[17]
b. Eczematous reactions
c. Acute renal failure which occurs with sucrose-formulations (not with sorbitol-stabilized preparations)
d. Rarely, thrombosis, and transient neutropenia
e. Acute myocardial infarction[19]
f. Aseptic meningitis
g. Post-infusion hyperproteinemia

SAFETY OF IMMUNOGLOBULIN IN PREGNANCY

IVIG can be given to pregnant women if there would be more benefits than risks for both the mother and the fetus.

IVIG is US FDA Pregnancy Category C. It has been used for many years during pregnancy for various immune disorders such as autoimmune thrombocytopenia, immune deficiency disorders, fetal-neonatal alloimmune thrombocytopenia, antiphospholipid syndrome (APAS), and recurrent pregnancy loss. A review done in 2001 revealed that IVIG is effective in the therapy of fetal-neonatal alloimmune thrombocytopenia. It is also promising in managing severe fetal-neonatal alloimmune hemolysis secondary to anti-erythrocyte antibodies. However, the same authors concluded that in the management of recurrent pregnancy loss, IVIG is not effective and warrants further studies.[19]

The Korean Society for Reproductive Immunology in 2017 recommends IVIG treatment among women with reproductive failure, including recurrent pregnancy loss and/or repeated implantation failure, who have cellular immune factors such as abnormal natural killer cell levels, natural killer cell cytotoxicity, and/or type 1 T-helper immunity.[20]

In view of the above-cited PSMID Guidance, IVIG has no use for pregnant women with severe COVID-19 disease.

SAFETY OF IMMUNOGLOBULIN IN BREASTFEEDING

IVIG can be offered to lactating women if there would be more benefits than risks to the breastfeeding infant.

Immunoglobulin (IgG) is naturally present in breast milk. Some data indicate that IgG concentrations in milk are normal or even higher and IgM titers in milk are

normal or lower during IVIG therapy.[21] There is a consensus that IVIG is a therapy of choice for lactating mothers afflicted with multiple sclerosis.[22]

A retrospective study done among 108 women suffering from multiple sclerosis, 69 received the drug postpartum. There were no serious adverse effects among breastfed infants whose mothers were given IVIG.[23] Another study was conducted among 24 postpartum women given IVIG for relapsing-remitting multiple sclerosis and was breastfeeding. There were no adverse effects seen among their infants.[24]

In view of the above-cited PSMID Guidance, IVIG has no use for lactating women with severe COVID-19 disease.

DOSAGE OF IMMUNOGLOBULIN FOR THE TREATMENT OF COVID-19

According to limited experience with use of this drug for the management of severe patients with COVID-19 pneumonia, and with the recommendation by the Philippine Society of Allergy, Asthma and Immunology, Inc. (PSAAI), IVIG has been noted to decrease levels of IL-1 receptor antagonists by about 1000x resulting to inhibition of tumor necrosis factor – alpha (TNF-α)-mediated cytotoxicity. And so IVIG may have clinical utility in the control of the initial phase of the cytokine storm in patients with severe COVID-19 infection, as adjunct to anti-inflammatory corticosteroid administration. It is best given between 7 to 14 days in the acute critical pneumonia stage in the following dosage regimens:[25]

a. As an adjunctive therapy at the 1st sign of respiratory depression with:
    1. Dyspnea, or
    2. RR > 30 cycles per minute, or
    3. SpO2 < 93%, or
    4. PaO2/FiO2 <300, or
    5. Progression of lung infiltrates > 50% within 24-48 hours

b. Suggested dose: 0.3-0.5 g/kg/day x 5 consecutive days

1. ***Start at 30ml/hr (0.5 ml/kg/hr), doubling the rate every 15 minutes up to maximum of 100ml/hr***
2. ***Consider adjustments per renal and cardiac status of the patient***

The PSAAI concluded that IVIG may have clinical advantage when started during the early course of the disease, though further trials are much needed to prove its efficacy and safety in this condition. The decision to utilize this preparation should take into consideration benefits and risks to the patient with severe disease, and to consider cost of therapy.[25]

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VII. MELATONIN

Melatonin is a hormone that regulates the sleep-wake cycle. It is primarily released by the pineal gland[1], but is currently marketed as supplement, used for the short-term treatment of sleep disorders such as from jet lag or shift work.[2] Melatonin is also used to treat delirium, atherosclerosis, respiratory disease and viral infections.[3]

Melatonin will have supportive adjuvant utility in treating COVID-19 induced pneumonia, Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) through the following mechanisms of actions:

1. Anti-inflammatory effects through several pathways
    a. Proper regulation of Sirtuin-1 (SIRT1) which inhibits high mobility group boxechromosomal protein 1 (HMGB1) leading to down-regulation of the polarization of macrophages towards the proinflammatory type.[4] This attenuates lung injury and inflammation.[5]
    b. Suppression of Nuclear factor kappa-B (NF-κB) activation in T cells and lung tissue, hence preventing ARDS [6,7]
    c. Up-regulation of NF-E2-related factor 2 (Nrf2) which protects lung, liver and heart from injury.[8]
    d. Reduction in the pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8, and an elevation in the level of anti-inflammatory cytokine IL-10.[9]
    e. Up-regulation of anti-oxidative enzymes (e.g. superoxide dismutase), down-regulation of pro-oxidative enzymes (e.g. nitric oxide synthase) and may interact directly with free radicals, functioning as free radical scavenger.[10,11]
    f. Enhancement of the immune response by improving proliferation and maturation of natural killing cells, T and B lymphocytes, granulocytes and monocytes in both bone marrow and other tissues.[12] Antigen presentation is also augmented in macrophages, where the up-regulation of complement receptor 3, MHC Class I and class II, and CD4 antigens were detected.[13]
    g. Suppression of NOD-like receptor 3 (NLRP3) inflammasome at the peak of infection protects the lungs from ALI/ARDS.[14]
    h. Mediates the suppression of VEGF in vascular endothelial cells, hence maintaining integrity of the vascular endothelial barrier, preventing edema and extravasation of the immune cells from blood vessels.[15]

2. Published studies also showed the following additional benefits of melatonin:
    a. Ameliorate septic shock via the NLRP3 pathway,[16] hence preventing sepsis-induced renal injury, septic cardiomyopathy and liver injury.[17]
    b. Have benefits in patients with myocardial infarction, hypertensive heart diseases, cardiomyopathy, and pulmonary hypertension.[18]

c. Neurological protection by reducing the cerebral inflammatory response, cerebral edema and brain-blood barrier permeability.[19]
d. In ICU patients, melatonin reduces the need for using drugs that causes deep sedation. It also decreases frequency of pain, agitation and anxiety[20] and improves sleep quality.[21]

3. Using immunomodulatory agents such as melatonin as an effective adjuvant besides vaccination. Since vaccine efficacy is inferior for the elderly and other high-risk groups, melatonin may amplify the production of cytokines needed for effective vaccine response.[27]

Drug Interactions: Other sedatives, Aspirin, OCPs, insulin and other OHAs, narcotic pain killers, antacids (lansoprazole, omeprazole), ondansetron, ADHD medications, cardiac and anti-hypertensive medications.

Pregnancy Category: Unknown

EFFICACY OF MELATONIN IN THE TREATMENT OF COVID-19

Limited evidence shows promising results for use of melatonin in therapy of COVID-19 disease. More studies are needed.

The rationale for the use of melatonin in COVID-19 patients not only focuses on the attenuation of the infection-induced respiratory disorders, but also an overall improvement and prevention of patients' wellbeing and potential complications.[22.] On literature review, majority of the studies done on melatonin are in-vitro or animal studies. Very few studies were done on humans (newborns with ARDS) which showed significant reduction of the pro-inflammatory cytokines and improved the clinical outcome.[25] Melatonin has various properties such as antioxidant, anti-inflammatory, anti-excitatory, sleep initiation and immunoregulation.[26] It is also well-known that melatonin counters the acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) induced by viral and bacterial infections.[27] Various evidence indicate that melatonin may play an important role in the treatment of COVID-19 when it is given prophylactically or therapeutically alone or in combination with other drugs. [28]

SAFETY ISSUES IN THE USE OF MELATONIN

When used in very high doses or under suppressed immune conditions, melatonin may induce increase production of pro-inflammatory cytokines.[23]

SAFETY OF MELATONIN IN PREGNANCY AND BREASTFEEDING

Due to lack of human studies, pregnant and breastfeeding women should not take exogenous melatonin at this moment.[24]

In a Cochrane study done in 2016, it was concluded that there was a lack of any completed randomised controlled trials, which assessed that melatonin given to the mother during pregnancy, can help protect the baby's brain. The authors concluded that further studies are needed.[26]

DOSAGE OF MELATONIN IN THE TREATMENT OF COVID-19

Melatonin is given at high dose at 36-72 mg/day in four divided doses.

In clinical trials, doses of 3 mg, 6 mg and 10 mg of melatonin oral intake by patients in ICU showed satisfactory safety when compared to placebo. Also, even when melatonin was given to humans at dose of 1 g/d for a month, there were no adverse reports of the treatment. [23]

The following dosages were derived from the MAC-19 PRO study of Dr. Castillo et al.[29]

For outpatient care

1. *Suspected, asymptomatic but with strong direct exposure to a COVID-19-positive patient:* Melatonin 3 mg/cap 3 caps 3x daily for 10 days, then 2 caps (6 mg) at bedtime subsequently.

2. *Asymptomatic or confirmed mild COVID-19 (no hypoxemia, no findings on chest X-ray):* Melatonin 3 mg/cap 4 caps 4x daily for 14 days then 3 caps 3x daily for another 14 days, then 2 caps (6 mg) at bedtime subsequently.

For inpatient care (hospitalized patients)

1. *Symptomatic COVID-19 or COVID-19-suspect on admission to hospital, with hypoxemia but no ARDS. Even if still unconfirmed but if with moderate symptoms (with hypoxemia, but no ARDS—ratio of partial pressure of oxygen to oxygen support given, or PFR, less than 300):* Give 100 mg of Melatonin ASAP initially then 4 mg/kbw/day (200-400 mg/day) in 3-4 divided doses for 1 week, then reduce to 2 mg/kbw/day (100-200 mg/day) in 3-4 divided doses for another week, then further reduce to 1 mg/kbw/day (50-100 mg/day) in 3-4 divided doses for another 2 weeks (total of 4-week treatment), then reduce to a maintenance dose of 2 caps (6 mg) at bedtime.

2. *COVID-19 or COVID-19-suspect on admission to hospital with mild ARDS (PFR less than 300 but more than 200). Even if still unconfirmed for COVID-19 but if with moderate symptoms and mild ARDS:* Give 150 mg Melatonin ASAP initially then 6 mg/kbw/day (300-600 mg/day) in 3-4 divided doses for 1 week, then reduce to 3 mg/kbw/day (150-300 mg/day) in 3-4 divided doses for another week, then further reduce to 1 mg/kbw/day (50-100 mg/day) in 3-4 divided doses for another 2 weeks (total of 4-week treatment), then reduce to a maintenance dose of 2 caps (6 mg) at bedtime.

3. *COVID-19 or COVID-19-suspect on admission to hospital with moderate to severe ARDS (PFR less than 200). Even if still unconfirmed for COVID-19 but if with severe symptoms and moderate to severe ARDS and not intubated yet:* Give 200 mg Melatonin ASAP initially then 8 mg/kbw/day (480-800 mgs/day) in 3-4 divided doses for 1 week, then reduce to 4 mg/kbw/day (200-400 mg/day) in 3-4 divided doses for another week, then further reduce to 1 mg/kbw/day (50-100 mg/day) in 3-4 divided doses for another 2 weeks (total of 4-week treatment), then reduce to a maintenance dose of 2 caps (6 mg) at bedtime.

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VIII. ZINC

Zinc is a mineral and an essential micronutrient. Zinc is a cofactor for polymerases and proteases involved in many cellular functions such as wound repair and intestinal epithelial cell regeneration. It has antioxidant properties and may protect against oxidative stress.[1] Zinc influences the immune system through enhancing innate and adaptive immunity. It increases chemotaxis and phagocytosis of polymorphonuclear cells and macrophages as initial response to infections. It also causes a decrease in the production of proinflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor (TNF). It also enhances the formation of premature and immature B cells to facilitate antibody production.[2]

Drug Interaction: Decrease absorption of antibiotics such as quinolones and tetracycline

Pregnancy Category: C

EFFICACY OF ZINC IN THE TREATMENT OF COVID-19

Further studies are needed to prove the efficacy of zinc in the therapy of COVID-19 and other related viral illnesses.

Majority of the studies are in the pediatric age group. Zinc reduces the severity and duration of acute and chronic diarrhea in children from developing countries.[1] Its supplementation was significantly associated with reducing the incidence and prevalence of pneumonia among children[35] Zinc has shown antiviral activity in various infections like influenza and the common cold[7,8]. It was shown to impair replication of a variety of RNA viruses. At low concentrations and in combination with pyrithione, inhibition of SARS-CoV replication has been observed.[6] In vitro studies have demonstrated that zinc can inhibit the enzymatic activity of SARS-CoV RNA polymerase and ACE2 activity[10]. Zinc may also have an effect on COVID-19 related symptoms like diarrhea and lower respiratory tract infection and can be used as an adjunct to monotherapy or as combination therapy with lopinavir-ritonavir, interferon, ribavirin and remdesivir[4,5]. Theoretically, inhibition of pro-inflammatory cytokines through the use of zinc may have a beneficial effect in reducing cytokine storm seen in patients with COVID-19.[9]

A meta-analysis done by Arentz et al.,[10] revealed a substantial volume of indirect clinical evidence from RCTs that zinc may potentially reduce the risk, duration and severity of COVID-19 particularly for populations at risk of zinc deficiency including people with chronic disease comorbidities and older adults. Pending any definitive evidence, clinicians may consider assessing the zinc status of patients with chronic disease comorbidities.

Benefits of zinc supplementation for the treatment of COVID-19 is unclear. There is limited indirect evidence that the use of zinc lozenges with daily dose of >75mg can shorten the duration of the common cold.

SAFETY ISSUES ON THE USE OF ZINC

Common adverse effects are gastrointestinal distress and irritation.

- Nausea and vomiting can occur in high doses. When taken in high dosage, zinc can cause decreased copper absorption resulting to anemia. In lozenge form, dosages > 100mg may cause permanent anosmia.

SAFETY OF ZINC IN PREGNANCY

Zinc can be given to pregnant women when the benefits outweigh the risks.

Zinc sulfate has been assigned to pregnancy category C by the FDA. Safety for use in pregnancy has not been established. The risk of fetal harm if used during pregnancy is remote.

On the contrary, reviews done showed that the use of zinc supplementation during pregnancy may improve pregnancy outcomes for both mother and infants. The evidence that maternal zinc supplementation lowers the risk of preterm birth is low, but its effect might be secondary to a reduction of maternal infection which is a primary cause of preterm birth.[3]

SAFETY OF ZINC IN BREASTFEEDING

Zinc can be given to lactating women when the benefits outweigh the risks.

Zinc can be secreted in breastmilk. Its levels decline in breastmilk during the first six months of exclusive breastfeeding. Maternal zinc supplementation may slow the rate of decline in its concentration. However, it appears that zinc intake alone will not have any major effects on breastmilk concentration. [4]

DOSAGE OF ZINC IN THE TREATMENT OF COVID-19

Zinc is given as 50 mg per orem daily.

In a paper written by Derward et al. regarding zinc supplemetation to enhance the efficacy of CQ/HCQ in the therapy of COVID-19, the authors stated that

comprehensive zinc dose findings studies may currently not be feasible as sufficient clinical safety needs to be ensured. They recommended administering zinc in the range of the upper limit of dosing based on recommended dietary allowances[10].

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IX. ASCORBIC ACID

Also known as L-ascorbic acid or L-ascorbate is a water-soluble vitamin that is found in a variety of foods and commonly sold as a dietary supplement. Vitamin C is required for the biosynthesis of collagen, L-carnitine. Collagen is an essential component of connective tissue, which plays a vital role in wound healing.[1] Aside from its biosynthetic and antioxidant functions, vitamin C plays a crucial role in immune function and improves the absorption of non-heme iron,[2] the form of iron present in plant-based foods. Insufficient vitamin C intake for prolonged periods causes scurvy, which is characterized by fatigue, widespread connective tissue weakness, and capillary fragility. In general, the daily recommended dietary allowances (RDAs) are: 90 mg for men, 75 mg for women, Pregnancy and Lactation 115 mg.[1,2]

Drug interactions: Barbiturates, Aluminum, Estrogens, Chemotherapies, Protease Inhibitors, Statins, Niacin, Warfarin.

Pregnancy Category: A

EFFICACY OF ASCORBIC ACID IN THE TREATMENT OF COVID-19

There are few evidences that show the efficacy of high dose ascorbic acid in the therapy of COVID-19. Further studies are needed.

Vitamin C has been proposed for treating respiratory infections when it was isolated several decades ago. It became particularly popular when Linus Pauling concluded from previous placebo-controlled trials that vitamin C can prevent and alleviate the common cold.

Based on a 2013 Cochrane review, regular supplementation of vitamin C has no effect on common cold incidence in the general population. This indicates that routine high dose intake is not rationally justified for community use. However, evidence show that in participants exposed to short periods of extreme physical stress and or cold environments, vitamin C reduced the risk of the common cold by 50%.[3]

Although varying amounts and duration of vitamin C supplementation were included in the review, the minimum amount was 200mg of vitamin C. The review also found that vitamin C supplements taken during a cold consistently reduces the duration of the illness by 8% in adults and 14% in children. It translates to shortening the duration by approximately 1 day.[3]

Among patients with sepsis and ARDS, high dose vitamin C infusion did not significantly reduce organ failure and biomarkers of inflammation and vascular injury compared with placebo. However, secondary outcomes show that the vitamin C group have a significant reduction in mortality at 28 days compared with the placebo group.[4] Re-evaluating the high dose infusion of vitamin C may be a timely choice for COVID-19 related ARDS.[5]

In a meta-analysis by Hemila, et al. vitamin C administered orally in doses of 1-3g/day reduced the length of ICU stay by 8.6% in 12 trials with 1, 766 patients. Vitamin C also shortened the duration of mechanical ventilation by 18.2% among patients needing mechanical ventilation for over 24 hours.[6]

As the COVID-19 situation is an evolving pandemic, a summary of therapeutic options is being proposed which includes vitamin C in the armamentarium.[7] Because of this, rescue therapy with high dose vitamin C may also be considered.[8]

SAFETY ISSUES IN THE USE OF ASCORBIC ACID

As a water-soluble vitamin, vitamin C poses little risk in regular amounts.

Ascorbic acid tablet dissolves completely once ingested, and any excess is excreted in the urine. In high doses, exceeding a daily level of 2000 mg, vitamin C has the potential to cause adverse reactions such as nausea, diarrhea and abdominal pain.[9] Also, at very high doses, it can cause calcium oxalate nephrolithiasis.[9, 10]

SAFETY OF ASCORBIC ACID IN PREGNANCY AND BREASTFEEDING

Vitamin C is safe for use during pregnancy and breastfeeding.

Vitamin C is classified as a US FDA Category A drug. However, current evidence does not support the routine use of vitamin C supplementation during pregnancy, as it does not improve outcomes (such as stillbirth, preterm birth, preeclampsia or low birthweight) for women and their pregnancy.[11]

A Cochrane review done in 2015 proved that routine supplementation with vitamin C during pregnancy does not improve outcomes for women and their babies. The author concluded that there was no convincing evidence that Vitamin C supplementation alone or in combination with other supplements results in other important benefits or harms[11.]

Until such time that high dose vitamin C be proven beneficial, it is prudent to follow the RDA for pregnant and lactating women at 85-120mg/day and not exceed the upper limit of 2 grams/day.[8]

DOSAGE OF ASCORBIC ACID FOR THE TREATMENT ON COVID-19

The proposed dosage from previous treatment regimens for high-dose intravenous vitamin C for COVID-19 is 50 mg/kg BW every 6 hours for 4 days with glucose restriction.

Several researches are looking into what benefit vitamin C may have among COVID-19 patients. Clinical trials are on-going as scientists in Wuhan, China and in New York, USA have been giving ultra-high doses of vitamin C, given intravenously, among COVID-19 patients. Results of these studies have yet to be published.

Concomitant hydrocortisone 50 mg IV every 6 hours for 7 days must be given to fight against therapy-induced inflammation.[5] Vitamin C is unlikely to prevent or cure a COVID-19 infection based on current evidence but studies seem to suggest that it may be a useful adjunct to fight off this viral infection.

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X. OSELTAMIVIR

Oseltamivir was originally used for the treatment of acute, uncomplicated influenza A or B illness. It is an antiviral neuraminidase inhibitor with potent and selective competitive inhibition of the influenza virus neuraminidase, an enzyme necessary for viral replication. Oseltamivir phosphate is an inactive prodrug that exerts pharmacologic activity when hydrolyzed in vivo to the active form. It interferes with the release of progeny influenza virus from infected host cells and stops spread of infection to new host cells. Oseltamivir reduces the duration of shedding and lowers the viral titers and can shorten the length of symptoms by 0.5 to 3 days.[1] Oseltamivir is a prodrug that is hydrolyzed by the liver to its active metabolite, oseltamivir carboxylate, with an elimination half-life of about 6–10 hours.[2] A study by Tanaka et al. using an ex vivo human placenta model showed that oseltamivir was extensively metabolized by the placenta however, transplacental transfer of the metabolite was incomplete with minimal accumulation on the fetal side.[2]

Drug interactions: Entecavir, methotrexate, probenecid and warfarin.

Pregnancy Category: C

EFFICACY OF OSELTAMIVIR IN THE TREATMENT OF COVID-19

Neuraminidase inhibitors are indicated for use in cases of influenza. Early oseltamivir administration may be considered in the primary management of COVID-19- suspected outpatients without hypoxia. Empiric use of oseltamivir should be discontinued once RT-PCR results are available.

During the ongoing COVID-19 outbreak, most patients who are symptomatic have used oseltamivir.[5] However, evidence from controlled trials on oseltamivir therapy is limited. A post-hoc exploratory analysis of a randomized controlled trial on the use of oseltamivir in the management of coronavirus infection (not including SARS-CoV-2) showed primary care patients with influenza-like illness recovered sooner when oseltamivir was added to the usual cate compared with usual care alone. The median time to recovery was shorter in patients randomized to oseltamivir: 4 days (interquartile range [IQR] 3–6) versus 5 days (IQR 3–8; hazard ratio 1.31; 95% confidence interval = 1.03 to 1.66; $P = 0.026$).[6]

In the study by Chiba involving 13 symptomatic patients given oseltamivir, results showed that oseltamivir administration made the temperature fall within 24hours. Clinical data were compared between patients receiving early treatment (ET) with oseltamivir, initiated within 24 hours, and patients administered late treatment (LT), initiated after this time point. Duration of fever was shorter in the ET group than in the LT group (33 ± 24 versus 94 ± 38 hours; $p < 0.01$). The time from fever onset to treatment initiation correlated with duration of fever ($r = 0.74$; $p < 0.01$) and the time

from peak to decline ($r = 0.55$; $p < 0.05$). This study concluded that early oseltamivir administration may lower the duration of fever in COVID-19- suspected outpatients without hypoxia when it is used in combination with antibacterial therapy.[7]

There is insufficient evidence to support the use of oseltamivir in the treatment of COVID-19 confirmed cases. Oseltamivir should only be continued in patients who are confirmed to have Influenza A or B. In vitro study showed that oseltamivir is ineffective against SARS-CoV-2.

Evidences supporting the use of oseltamivir in confirmed cases of COVID-19 were mostly case series and case reports from China. However, these are not controlled studies, and results may have been confounded by the concomitant use of a combination of antibiotics, corticosteroids, gammaglobulin and other antivirals.

SUPPORTING STUDIES:

1) Cohort of 41 admitted patients with laboratory-confirmed SARS-CoV-2 infection in Wuhan, China [8]	• 38 or 93% were given Oseltamivir in addition to a combination of antibiotics. • In the ICU setting, 12 or 92% were given Oseltamivir, while 26 or 93% were given in the non-ICU setting, with a total of 6 deaths.[9]
2) Cohort of 138 patients hospitalized in Wuhan, China [9]	• 90% of patients received Oseltamivir, in combination with antibiotics such as Ceftriaxone, Moxifloxacin and Azithromycin. • 85 patients (61.6%) were still admitted, 47 patients (34%) were discharged and 6 patients (4.3%) died. • 9.4% required additional vasopressors and 1.44% required renal replacement therapy. • The severity of disease was an important determinant of antiviral and corticosteroid therapy. However, no effective outcomes were observed.
3) Cohort of 99 patients of 2019 novel coronavirus pneumonia in Wuhan, China [10]	• All patients were treated in isolation. • Antiviral therapy was given to 76% (75 patients) in the form of either oral oseltamivir or IV ganciclovir and lopinavir/ritonavir tablets. • The duration of antiviral therapy ranged from 3 to 14 days. 70 patients received antibiotic treatment for 3-14 days, and 19 patients (19%) were also treated with additional corticosteroids for a duration of 3-15 days. • Out of the 99 patients, 31 patients (31%) were discharged, and 11 (11%) died.
4) Case report of 2 patients with SARS-CooV-2 pneumonia in Wuhan, China [11]	• Both patients were treated with IV corticosteroids, human gammaglobulin, antibiotics (Moxifloxacin) and antiviral (Oseltamivir and Abidol hydrochloride) and Chinese herbal medicine (Tanreqing IV gtt). Both patients recovered.

An in vitro study was performed by Tan et al. to evaluate the antiviral efficiency of oseltamivir specifically against SARS-CoV-2. An analysis of molecular docking showed that oseltamivir carboxylic acid effectively binds to the active site of 3CL pro (3C-like protease). However, its inhibitory effect against SARS-CoV-2 was not strong. They concluded that oseltamivir is ineffective against SARS-CoV-2 *in vitro* study and the clinical use of oseltamivir did not improve the patients' signs and symptoms and did not slow the disease progression.[5]

SAFETY ISSUES ON THE USE OF OSELTAMIVIR

Oseltamivir is generally well tolerated but there are associated mild to moderate adverse events.

The common side effects of oseltamivir are nausea (10%), vomiting (2-15%), abdominal pain, diarrhea, headache, insomnia, vertigo. The meta-analyses by Santesso et al. shows that in clinical trials of oseltamivir, adverse events (AEs) in adults and children were generally mild or moderate, the most common being nausea and vomiting during the first 1 to 2 days of treatment. As with many other medications, however, further data on adverse effects have been generated from post-marketing reports. Rare adverse effects reported include serious skin hypersensitivity reactions, cardiac arrhythmias, and neuropsychiatric episodes. Previous analyses of healthcare claim databases have, however, suggested that the risks of these events were no more than the risk in the general population.[12] The study by Blumental and Song noted that there was no increase in CNS-related and neuropsychiatric events among adults, children, or adolescents with influenza who were prescribed oseltamivir.[13]

Known allergies or hypersensitivities are a contraindication to oseltamivir use. It should be used cautiously in patients with hereditary fructose intolerance.[3]

SAFETY OF OSELTAMIVIR IN PREGNANCY

Designated as Pregnancy Class C, Oseltamivir may be used during pregnancy.

Oseltamivir is used to treat influenza and to provide post-exposure prophylaxis. There are no controlled data in human pregnancy but post-marketing reports and observational studies showed no malformations nor fetal/ neonatal toxicity by this drug.[1]

In the study by Ehrenstein et al. including 946, 176 pregnancies, there was no evidence of an association between prenatal exposure to oseltamivir and any of the

birth outcomes assessed (congenital malformations, fetal death, preterm birth, fetal growth, and low 5-min Apgar score). Of these, 449 had first-trimester exposure and 1449 had second/third-trimester exposure to oseltamivir. Adjusted ORs following first-trimester exposure were 0.94 (95% CI 0.49 to 1.83) for any major congenital malformation and 1.75 (95% CI 0.51 to 5.98) for congenital heart defects, based on 7 exposed cases.[14] These were noted to be no more than what is observed in the general population.

SAFETY OF OSELTAMIVIR IN BREASTFEEDING

Oseltamivir is safe for breastfeeding mothers. It is excreted in low levels into human milk and is not expected to cause harmful effects in the nursing infants.

According to Huang et al., the transfer rates of Oseltamivir and Oseltamivir carboxylate, its metabolite, were low at 12.39% and 10.17%, respectively.[15,16] Large retrospective studies did not show risks for any major congenital malformations and heart defects. There was no evidence of increased risk for preterm birth or small for gestational age infants.[17]

DOSAGE OF OSELTAMIVIR FOR THE TREATMENT OF COVID-19

Oseltamivir is given at a dose of 75mg tablet taken twice a day for 5 days. Same dose is used for pregnant and lactating mothers. Once PCR results prove positive for SARS-CoV-2 and/or negative for influenza, Oseltamivir should be discontinued.

The therapeutic oral dosage for influenza, including novel H1N1 influenza, for adults is 75 mg taken twice daily for 5 days, starting within 48 hours of the initial symptoms to capture the early phase of viral replication.[2] The same daily dosing of 75mg twice daily was used for hospitalized 2019-nCoV pneumonia patients in Wuhan, China, as well as for pregnant and lactating mothers.[10] For chemoprophylaxis, the recommended dosage is 75 mg taken once daily for 10 days after exposure.[2]

For patients with kidney impairment, the treatment dosing adjustments for creatinine clearance is as follows:[1]

CrCl = 30-60 mL/min	30mg twice daily
CrCl less than 30 mL/min	30mg daily
Hemodialysis patients	30mg after dialysis x 5 days

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XI. LOPINAVIR / RITONAVIR

Lopinavir is a protease inhibitor used to treat HIV infection, with ritonavir as a booster. It has been widely used in treating patients with human immunodeficiency virus. The standard dose in pregnant women is LPV/r 400 mg/100 mg twice daily.

HIV protease is a 99-amino-acid, aspartic acid protein which is responsible for maturation of virus particles late in the viral life cycle. HIV protease systematically cleaves individual proteins into functional subunits for viral capsid formation during or shortly after viral budding from an infected cell. HIV protease inhibitors function as competitive inhibitors that directly bind to HIV protease and prevent subsequent cleavage of polypeptides They exhibit activity against clinical isolates of both HIV-1 and HIV-2.[1]

Drug-drug interaction: Lopinavir/ritonavir is anticipated to have varying degrees of interaction with other medications that are also CYP3A and/or P-gp substrates.[2] Some products that may interact with this drug include: cobicistat, certain HIV medications (fosamprenavir, tipranavir), orlistat, boceprevir, rifampin, alpha blockers (alfuzosin, tamsulosin), fluticasone, salmeterol, cisapride, sildenafil, tadalafil, ergot drugs (ergotamine, dihydroergotamine), pimozide, rivaroxaban, simeprevir, certain sedatives (midazolam, triazolam) and statins (lovastatin, simvastatin).

Pregnancy Category: C

EFFICACY OF LOPINAVIR/RITONAVIR IN THE TREATMENT OF COVID-19

More studies are needed to prove the efficacy of Lopinavir-Ritonavir in the therapy of COVID-19 and other related viral illnesses.

Lopinavir/ritonavir was used as treatment for Severe Acute Respiratory Distress Syndrome (SARS) caused by a coronavirus in 2003. In the study by Chu et.al. involving 152 patients with SARS found that compared with ribavirin alone, patients treated with lopinavir/ritonavir and ribavirin had lower risk of acute respiratory distress syndrome (ARDS) or death.[3] Sheahan et.al. compared the efficacy of lopinavir, ritonavir and interferon alpha versus remdesivir against the Middle East Respiratory Syndrome (MERS)-CoV, another coronavirus. Remdesivir was effective in reducing the virus titer of mice infected and improving the lung tissue damage. Its effect is better than that of the Lopinavir/Ritonavir combined with interferon-β treatment group.[4]

The First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU) used lopinavir/ritonavir (2 capsules, po q12h) combined with arbidol (200 mg po q12h) as

the basic regimen against SARS-COV2. In their treatment experience on 49 patients, the average time to achieve negative viral nucleic acid test for the first time was 12 days (95% CI: 8-15 days). The duration of negative nucleic acid test result (negative for more than 2 times consecutively with interval ≥ 24h) was 13.5 days (95% CI: 9.5 - 17.5 days). In their protocol, when the basic regimen is not effective, chloroquine phosphate was used on adults between 18-65 years old (weight ≥ 50 kg: 500 mg bid; weight ≤50 kg: 500 mg bid for first two days, 500 mg qid for following five days).The incidence of abnormal liver function test was 51.9% in COVID-19 patients who received lopinavir/ritonavir combined arbidol antiviral treatment.[5]

A randomized, controlled, open-label trial of hospitalized adults (n=199) with confirmed SARS-CoV-2 infection, enrolled patients who had oxygen saturation of 94% or less on ambient air or PaO_2 of less than 300 mm Hg. These patients were randomized to receive lopinavir/ritonavir 400 mg/100 mg PO BID for 14 days added to standard care (n=99) or standard care alone (n=100). Standard care involved, as necessary, giving of supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO). Results showed that time to clinical improvement did not differ between the two groups (16 vs. 16 days, HR 1.31, 95% CI 0.95-1.85, p=0.09). The mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%) but did not reach statistical significance. Lopinavir-ritonavir was associated with a statistically shorter time to clinical improvement when started early within 12 days after the onset of symptoms (HR 1.25, 95% CI 1.77 to 2.05, median not reported). They concluded that in hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Fourteen percent of patients in the intervention group could not complete their 14-day course mainly due to gastrointestinal side effects.[6]

A closer look at the data of Cao et al. by Owa would show that the mortality rate in the LPV/r group was 5.8% lower than the standard care group. While the 5.8% is not statistically significant among 199 patients, if the same result is obtained in 1000 participants, this would be significant. In addition, the LPV/r group had a shorter hospital stay (median of 6 days) compared to the 11 days for the standard care group[7]

LPV/r is an option for COVID 19 cases with prolonged QT interval, arrhythmias, elevated AST or ALT >5x, G6PD deficiency, hypersensitivity to CQ or HCQ and decompensated heart failure.[8]

The World Health Organization discontinued the use of lopinavir/ritonavir in the Solidarity trial in hospitalized patients on July 4, 2020. The interim results released mid-October 2020 found LPV/r (with or without interferon) appeared to have little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality,

initiation of ventilation, and duration of hospital stay. Death rate ratios were: lopinavir RR = 1.00 (0.79-1.25, p = 0.97; 148/1399 vs 146/1372) and lopinavir plus interferon RR=1.16 (0.96-1.39, p = 0.11; 243/2050 vs 216/2050).[9]

On October 2020, the randomized evaluation of COVID-19 therapy (RECOVERY) trial released its data on the use of LPV/r 400mg/100 mg BID. This was an investigator-initiated, individually randomized, open-label, platform trial that evaluated the effects of potential treatments in patients admitted to hospitals with COVID-19 in the United Kingdom which started March 19, 2020. A total of 1616 patients were allocated in the LPV/r group and 3424 patients in the usual care group. A quarter of the patients had no ventilatory support, most were receiving oxygen only and a very small proportion were on invasive mechanical ventilation. Allocation to LPV/r was associated with a similar time until discharge alive from hospital as usual care (median 11 days [IQR 5 to >28] in both groups) and a similar probability of discharge alive from hospital within 28 days (rate ratio 0·98, 95% CI 0·91–1·05; p=0·53). Among individuals not on invasive mechanical ventilation at baseline, the number of patients who progressed to the pre-specified composite secondary outcome of invasive mechanical ventilation or death among those allocated to LPV/r was similar to that among those allocated to usual care (risk ratio 1·09, 0·99–1·20; p=0·092). In patients admitted to hospital with COVID-19, LPV/r was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death. Enrolment of participants to the LPV/r group was closed on June 29, 2020.[10]

SAFETY ISSUES ON THE USE OF LOPINAVIR/RITONAVIR

The main adverse reactions were diarrhea, nausea, vomiting, increase in serum aminotransferase, jaundice, dyslipidemia and increase of lactic acid in the 49 COVID 19 patients who were given LPV/r.[5]

Precautions: History of liver disease, patients with chronic Hepatitis B or C, redistribution accumulation or loss of body fat may occur.[11]

The French Perinatal Cohort found no association between birth defects and LPV or RTV use with 85% power to detect a 1.5-fold increase.[12] The Pediatric HIV/AIDS Cohort Study found no association between LPV and congenital anomalies.[13] In a 10-year surveillance data from the United Kingdom and Ireland, among LPV-exposed pregnancies, the overall congenital abnormality rate was 2.9% (134 infants out 4,609 LPV-exposed pregnancies). This rate is comparable to rates of congenital abnormalities observed in populations without HIV.[14] Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.1% compared with a prevalence of either 2.7% when using

data from the Metropolitan Atlanta Congenital Defects Program (MACDP) or 4.2% when using data from the Texas Birth Defects Registry (TBDR).[15]

SAFETY OF LOPINAVIR/RITONAVIR IN PREGNANCY

Among HIV pregnant women given this drug combination, there have been reports of increased risk of preterm delivery. More studies are needed to prove the safety and efficacy of LPV/r for COVID-19 treatment among pregnant women.

LPV/r has been widely used in the treatment of HIV in pregnant women. A study in China found that women who received PI-based regimens had higher rates of preterm birth than those who received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.[16] A similar finding was noted in the United Kingdom/Ireland National Study of HIV in Pregnancy and Childhood. In this study, 38.9% of women (2,368 out of 6,073) who took LPV/r during their pregnancies carried a greater risk of preterm delivery than the use of NNRTI-based regimens.[17]

SAFETY OF LOINAVIR/RITONAVIR IN BREASTFEEDING

Amounts of LPV/r in breastmilk are not clinically significant.

In a study of 51 mother-infant pairs in Uganda where the mother received LPV/r during pregnancy and breastfeeding, transfer during breastfeeding was not observed, and no infant had detectable plasma LPV levels at 12 weeks. LPV concentrations in human breast milk are very low to undetectable and LPV concentrations in breastfeeding infants whose mothers received LPV are not clinically significant.[18-21]

DOSAGE OF LOPINAVIR/RITONAVIR FOR THE TREATMENT OF COVID-19 INFECTION

The dose is 200mg/50mg tablet 2 tablets BID po x 14 days.

There are 16 on going trials with use of LPV/r in the management of SARS-CoV-2.[8]

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XII. FAVIPIRAVIR

Favipiravir is previously known as T-705, is a prodrug of a purine nucleotide, favipiravirribofuranosyl-5′-triphosphate. This drug works by inhibiting the RNA polymerase, halting viral replication. Most of preclinical data on favipiravir are derived from its influenza and Ebola activity. However, it also demonstrated broad activity against other RNA viruses.[1] This drug is currently available in Japan for the treatment of influenza since 2014.

Drug Interactions: CYP2C8 and aldehyde oxidase inhibitor

Pregnancy Category: X

EFFICACY OF FAVIPIRAVIR IN THE TREATMENT OF COVID-19

More studies are needed to prove the efficacy of Favipiravir in the management of COVID-19.

There is currently limited data supporting the use of Favipiravir as treatment for COVID-19. In a prospective, randomized, multicenter study, favipiravir (n = 120) was compared with umefinovir (brand name Arbidol) (n = 120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, P = .019). No significant differences were observed in the severe or severe and moderate (combined) arms.[2]

Favipiravir was also successfully used for the post-exposure prophylaxis and treatment of patients with Ebola virus infection[3,4] and influenza.[5] During the 2014 epidemic of Ebola virus infection in West Africa, two studies were done. The control group were patients who were treated without favipiravir in the period before favipiravir treatment became available; and the treatment group were those who received favipiravir. The first is an Ebola study conducted in Guinea included 126 patients, and 111 were analyzed and compared with 540 patients as a historical control group. Favipiravir treatment reduced the mortality rate in the low viral load group to 33% compared with the historical control group that was not treated with favipiravir, but this reduction in the mortality rate was not statistically significant.[6] The second Ebola study was conducted in Sierra Leone included 39 favipiravir-treated patients and 85 historical control patients. The overall survival rate in the favipiravir treatment group was higher than the control group (56.4% [22/39] vs 35.3% [30/85]; P = .027).[3]

SAFETY ISSUES ON THE USE OF FAVIPIRAVIR

Favipiravir has minimal side effects. This drug has mild adverse effect profile and is overall well-tolerated, although the adverse event profile for higher-dose regimens is limited.[7,8] Most commonly observed side effects are hyperuricemia, diarrhea, elevated transaminases, and reduction in neutrophil count.

SAFETY OF FAVIPIRAVIR FOR PREGNANT WOMEN AND BREASTFEEDING

Favipiravir is contraindicated among pregnant and lactating women.

This drug is contraindicated in pregnant patients since it has been shown to cause congenital anomalies in animals. Its metabolite is excreted in breastmilk.[9]

DOSAGE OF FAVIPIRAVIR FOR THE TREATMENF OF COVID-19

Favipiravir is given with loading of 2400 mg to 3000 mg every 12 hours for 2 doses, followed by a maintenance dose of 1200 mg to 1800 mg every 12 hours.

It comes in 200 mg/tablet and can be given crushed or mixed with liquid. Its bioavailability is >95%. No renal adjustment is needed.[9]

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XIII. RIBAVIRIN

Ribavirin is a unique guanosine analogue with broad-spectrum activity against many RNA and DNA viruses. It is a 1-ribosyltriazole that is the 1-ribofuranosyl derivative of 1,2,4-triazole-3-carboxamide. As a nucleoside analogue, it can mimic the structure of a natural nucleoside such that it is recognized by cellular or viral enzymes, however due to modifications to their structure, leads to disruption and/or termination of replication or other biological processes.[1]

The following are the **mechanisms of action** of Ribavirin:

1. Inhibition of inosine monophosphate dehydrogenase (IMPDH) resulting in intracellular guanosine triphosphate (GTP) depletion occurs at lower ribavirin concentrations (10μM ribavirin). Reduced intracellular GTP secondarily may result in inhibition of mRNA capping and impact on host cell gene expression, inflammation and immunomodulation.
2. Inhibition of viral RNA dependent RNA polymerase
3. Enhancement of viral mutagenesis, which occurs at higher ribavirin concentrations in vitro (≥100μM), by means of the incorrect substitution of ribavirin triphosphate for GTP.[2]

Drug Interaction

1. In vitro and in vivo antiviral activity of ribavirin against some viruses (eg, influenza virus) may be enhanced by other antiviral agents (eg, amantadine, rimantadine).[3]
2. Ribavirin may antagonize the in vitro antiviral activity of stavudine and zidovudine against HIV; concomitant use of ribavirin with either of these drugs should be avoided.[3]
3. The co-administration of didanosine with oral ribavirin is not recommended. There were cases of fatal hepatic failure, peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials. Ribavirin appears to potentiate the antiretroviral effects of didanosine by promoting formation of didanosine-S'-triphosphate, the metabolically active metabolite of didanosine with antiviral activity.[3]
4. Results of in vitro tests in various cell cultures and peripheral blood lymphocytes indicate that ribavirin may potentiate the antiretroviral activity of didanosine against human immunodeficiency virus (HIV; formerly HTLV-III/LAV) and Moloney murine sarcoma virus.[3]
5. Conversely, results of in vitro tests indicate that ribavirin antagonizes the antiviral activity of zidovudine and zalcitabine against HIV. The mechanism by which ribavirin antagonizes the antiretroviral effects of zidovudine or zalcitabine has not been elucidated to date but it has been suggested that ribavirin may interfere with phosphorylation steps that convert the drugs to

their active triphosphate metabolites, deoxythymidine triphosphate or dideoxycytidine-S'-triphosphate, respectively.[3]

Pregnancy Category: X

EFFICACY OF RIBAVIRIN IN THE TREATMENT OF COVID-19

Ribavirin is currently not considered a viable drug in the therapy of SARS-CoV-2 infection due to lack of efficacy and associated side effects with the high doses needed to be given to patients afflicted with the condition.

Ribavirin was evaluated against SARS-CoV-1 in 2003 and used clinically in combination with corticosteroids and/or interferon in the absence of other treatment options; however, outcomes were either poor or ill-defined. The doses required for antiviral activity against SARS range from 1.2 gm to 2.4 gm by mouth every 8 hours, which are associated with excessive toxicity to patients. Wang and colleagues evaluated the in vitro activity of ribavirin against SARS-CoV-2 and found an EC50 of 109.5μM, which was over 100 times less potent than remdesivir. The risk of hematologic toxicity at high doses likely outweighs potential clinical benefit, and therefore ribavirin was not considered a viable candidate for further investigation by the World Health Organization research and development plan for SARS-CoV-2 given lack of in vitro efficacy, toxicity profile, and poor outcomes.[4]

SAFETY ISSUES ON THE USE OF RIBAVIRIN

Ribavirin is contraindicated during pregnancy and breastfeeding due to its potential teratogenicity demonstrated in all animal models studied. Avoidance of pregnancy for 4 months after ribavirin exposure for treated women and for 7 months for female partners of treated men is therefore recommended, although preliminary analysis of the Ribavirin Pregnancy Registry established in 2003 has not been able to demonstrate any clear evidence for human teratogenicity for ribavirin.

Rivabirin and PEG-Interferon Alfa-2A dual therapy is associated with flu-like symptoms, depression, suicide, insomnia, irritability, relapse of drug abuse/overdose, hepatic decompensation in 2% of HIV co-infected patients and bacterial infections each occurring at a frequency of less than 1%. Ribavirin-induced anemia is a dose-dependent adverse effect where reduced hemoglobin levels can be seen within the first 1-2 weeks in therapy. The mechanism of ribavirin-induced anemia has been shown to involve reductions in reticulocyte counts and erythrocyte Na-K pump activity, and increases in K-Cl co-transport.[2,3]

SAFETY OF RIBAVIRIN IN PREGNANCY

Ribavirin is contraindicated in pregnancy.

Avoidance of pregnancy for 4 months after ribavirin exposure for treated women and for 7 months for female partners of treated men is recommended.

SAFETY OF RIBAVIRIN IN BREASTFEEDING

Ribavirin is contraindicated in breastfeeding women.

DOSAGE OF RIBAVIRIN IN THE TREATMENT OF COVID-19

Ribavirin is given at 1.2 to 2.4 grams per orem every 8 hours.

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XIV. INTERFERON

Interferon is a biologic response modifier/cytokine. There are three types of interferons (IFN), alpha, beta and gamma. IFN has antiviral activity and also various kinds of biological activities including cell growth inhibition, immunosuppressive effects, enhancement of macrophage, natural killer (NK) cell, killer (K) cell and neutrophil function , and cell differentiation-inducing activity.[1] Interferons (IFNs) were the first therapeutic agents that permitted successful antiviral therapy with acceptable side effects in patients with chronic hepatitis B, D, and C.[2]

Although interferon (IFN) has been used as a treatment for chronic hepatitis B virus (HBV) infection for 40 years, its exact mechanisms of action are still unclear. Interferon is thought to induce specific genes that interfere with several steps in the HBV lifecycle, including virus entry; uncoating of the virion; transcription of viral DNA into RNA; translation of viral RNA into proteins; and assembly of nucleoplasmids. It may also augment cell-mediated immunity, thereby promoting clearance of HBV-infected hepatocytes.[3]

It is assumed that increased expression of antiviral genes induced by type 1 IFNs is an important factor in the elimination of hepatitis viruses. These antiviral genes are only partially understood with respect to function.[4]

Control of hepatitis B is only rarely achieved in patients with an incompetent immune system, the immunostimulatory properties of type 1 IFNs are probably required to eliminate the hepatitis B virus.[4]

Drug Interactions: Barbiturates (e.g. phenobarbital), Colchicine, Chemotherapeutic drugs (e.g. aldesleukin, cyclosporine), Hydroxyurea, Telbivudine, Theophyllines (e.g. aminophylline) [5,6]

Pregnancy Category: C

EFFICACY OF INTERFERON IN THE TREATMENT OF COVID-19

Further studies are needed to prove the efficacy of interferon in the therapy of COVID-19 and other viral illnesses.

Interferons have shown to possess a crucial role in the defense against coronavirus diseases. The virus can impede the interferon induction in humans. Moreover, STAT1, a key protein in the interferon mediated immune response, is antagonized by the virus. This could explain the increased response threshold of immune cells to IFNs during CoV infections.[7]

Patients with SARS-CoV-2 at the late stages of the disease suffer from many abnormalities, which are the result of immune system imbalance and malfunction and lack of effective IFN-specific immune responses that can lead to pro-inflammatory reactions and immunopathological conditions, presented by lethal inflammations in the lungs and vascular leakage.[8]

The key for success in reducing the disease fatality might be the stimulation of the innate immune responses to trigger IFN production at the very early stages of the disease, which might be done through administration of agents that are able to augment IFNs production.[8]

SAFETY ISSUES ON THE USE OF INTERFERON

Various systemic side effects are associated with the use of interferon.

The lack of data on safety of interferon use for treatment of COVID-19 infection, warrants further investigation. However, a wide array of adverse effects of alpha interferon treatment have been described in chronic hepatitis C patients. Several side effects such as fever, headache, fatigue, arthralgias, and myalgias are common specially with initial injections, as interferon treatment for chronic hepatitis C infection is administered by subcutaneous or intramuscular injection.[9]

Neuropsychiatric side effects such as depression and irritability can be most troublesome, their mechanisms are not well understood. IFN treatment can induce autoimmune thyroiditis with either hypothyroidism or hyperthyroidism.[9]

SAFETY OF INTERFERON IN PREGNANCY

Few data show no associated increase in rate of congenital anomaly formation with use of interferon during pregnancy. More studies are needed to prove its safety in pregnancy.

Currently, limited data are available on pregnancy outcomes in patients exposed to interferon-beta (IFN-beta) before or during pregnancy. However, recent European IFN-beta Pregnancy Registry released a cumulative pregnancy exposure data and prevalence of pregnancy and infant outcomes in IFN-beta-exposed pregnant women between years 2009 to 2017.[10] The data gathered from these cases suggest no evidence that IFN-beta exposure before conception and/or during pregnancy adversely increases the rate of congenital anomalies or spontaneous abortions.[10]

SAFETY OF INTERFERON IN BREASTFEEDING

Further studies are needed to prove the safety of interferon among lactating women.

A decision should be made to discontinue breastfeeding or discontinue interferon, taking into account the importance of the drug to the mother. Excretion of interferon into human milk is unknown.[11]

DOSAGE INTERFERON IN THE TREATMENT OF COVID-19

Interferon has been administered as 5 million units of interferon-α or its equivalent as twice daily, given in 2 mL of sterile water by nebulization.

Despite the evidences for the efficacy of IFNs in treating CoV-induced infections, the proper dosing and ideal timing for such interventions needs to be verified in clinical trials. Moreover, adding IFN-γ to an IFN-I as a combination therapy is strongly suggested.[8]

Based on COVID-19 clinical experience released by American Society of Health-System Pharmacists (ASHP), there are data accumulating on lopinavir/ritonavir (LPV/RTV) used with or without interferon in patients with COVID-19 outside of clinical trials wherein they used 5 million units of interferon-α or equivalent twice daily given in 2mL of sterile water by nebulization.[12]

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XV. AZITHROMYCIN

Azithromycin belongs to the macrolide antibiotic class. It has a broad spectrum of action against various Gram-positive and Gram-negative bacteria. The activity extends to *Legionella* species, *Bordetella pertussis*, *Mycoplasma pneumonia*, *Chlamydia*, *Treponema pallidum*, and *Mycobacterium avium* complex.[1] This antimicrobial agent is bacteriostatic as it exhibits reversible binding to bacterial ribosome thus inhibiting protein synthesis.[2] Azithromycin possesses a rather long half-life because of uptake in lung tissue, tonsil, and in men, in the prostate glands. The oral bioavailability is 35 to 42% among healthy people. Average concentrations in the tissues are 10 to 100-fold higher than in serum and may persist for many days.[1] This antibiotic is usually given by oral route though a parenteral form is also in use for those who cannot tolerate per orem intake. The duration of intake varies depending on the disease condition and the severity of illness and as such, guidelines are instituted which have been based on years of research.[3]

Compared with clarithromycin, azithromycin does not interact with cytochrome P450 3A4 enzyme system. Azithromycin is also stable in acid conditions, and so it can be given with food. General indications include treatment of Chlamydial cervicitis, pelvic inflammatory disease (PID), trachoma infection, upper and lower respiratory tract infections, and as prophylaxis against opportunistic *Mycobacterium avium* complex infection among those with human immunodeficiency virus (HIV) disease. It is also effective in the therapy of chancroid, granuloma inguinale, bacterial enteritis secondary to *Campylobacter* and *Salmonella* species, and cholera.[4]

Some in vitro and animal research has demonstrated immunomodulatory or anti-inflammatory effects of azithromycin. Previous data have shown efficacy in therapy of diffuse bronchiolitis wherein macrolides have been shown to improve lung function and prognosis. Macrolides were also beneficial in the management of cystic fibrosis. In particular, azithromycin has been effective in improving lung function at seven months in patients who had lung transplant for bronchiolitis obliterans.[5,6] Because of these reports, azithromycin and other macrolides have been suggested as therapy for sepsis and epidemic viral infections involving the respiratory tract to prevent cytokine storm. Its use for cytokine storm, however, is controversial especially concerning antimicrobial resistance and limited clinical evidence.[1]

Drug Interactions: Azithromycin interacts with nelfinavir (increased azithromycin), and warfarin (potentiation of warfarin anticoagulant effects). Significant potentiation occurs with concomitant intake of the following drugs, and as such, concurrent administration is avoided:[7] Cisapride, Dihydroergotamine, Dronedarone, Methylergonovine, Piperaquine, Saquinavir, Terfenadine, Thioridazine, Ziprasidone.

Pregnancy Category: B

EFFICACY OF AZITHROMYCIN IN THE TREATMENT OF COVID-19 INFECTION

A latest study demonstrated that the addition of azithromycin to existing regimens does not improve outcomes.

Azithromycin has always been used in combination with hydroxychloroquine (HCQ) in the treatment of SARS-CoV-2 or COVID-19 infection. At current time, there have been opposing conclusions from the French studies with regard to viral clearance and clinical utility.[8] In a study by Molina et al., use of HCQ plus azithromycin did not show a significant antiviral effect of this drug combination. HCQ (at 600mg per day for 10 days) was given with azithromycin (at 500mg on day 1, 250mg on days 2-5) to eleven patients with mean age of 58.7 years. Most of the patients had comorbid conditions (8 out of 11), and they had poor outcomes. Both drugs were stopped in a patient for prolonged QT interval. PCR tests for the virus remained positive in 80% of patients after 5-6 days of therapy.[9]

In another study in France included azithromycin in the regimen together with hydroxychloroquine, among twenty patients against a control group of sixteen patients who got standard of care. The patients received HCQ at 200mg 3x a day who showed nasopharyngeal viral clearance on 6th day. Six patients were excluded due to incomplete data and 4 out of these excluded patients had either ICU admission or death. Azithromycin was also added to 6 patients for possible bacterial superinfection at 500 mg on day 1 then followed by 250 mg daily for 4 days. There was 100% viral clearance among those given azithromycin though this warrants further analysis since these patients who received combination HCQ + azithromycin were the ones who had lower viral loads.[10] The same French doctors went through with their study of combining HCQ and azithromycin among 80 patients. Sixty-five of these patients met the criteria of having a favorable outcome. While the results of this particular study seem promising, there were many flaws because the study had no control group, and the results did not differentiate between asymptomatic carriers and patients having high or low viral load.

An ongoing trial named The RECOVERY Trial (Randomized Evaluation of COVID-19 Therapy) is being done in the United Kingdom presently. HCQ and azithromycin are being tested separately initially, and then if there is any effect among subjects given alone, compared to those without drugs, they can be combined later. We will still await results from this large trial.[12]

The COVID-19 Treatment Guidelines Panel of the National Institutes of Health (NIH) "recommends against the use of HCQ plus azithromycin for the treatment of COVID-

19, except in the context of a clinical trial."[13] From the Clinical Practice Guidelines (CPG) for COVID-19 formulated by the Philippine Society for Microbiology and Infectious Diseases (PSMID), it is stated that "the known toxicities of both medications (HCQ and azithromycin) should be weighed against the potential benefit of eliminating viral load, decreasing infectivity, and improving clinical outcomes in patients who are otherwise have no way of combating the pandemic. With the view that the combination may save lives (HCQ and azithromycin), hence relieving the healthcare system temporarily, the medication should be offered to patients and decision-making shared between them and their healthcare professional…critical monitoring of hospital course and expected adverse events is warranted."[14] Based on these statements the PSMID recommends use of azithromycin in combination of HCQ in clinical conditions when the healthcare provider assesses that there would be more benefit than harm and advises monitoring of side effects. The group also concluded that more studies with bigger sample sizes are needed.

The results of COALITION II, a study done in Brazil is an open-label randomized trial looking into azithromycin in addition to standard of care, that included hydroxychloroquine, compared to standard of care alone in patients with severe COVID-19. The major strength of this trial is that it was randomized, and this eliminated the confounding by indication inherent in observational analyses. ***In this study it was shown that the addition of azithromycin to existing regimens does not improve outcomes***. Avoiding use of azithromycin in severe COIVD cases will contribute to the prevention of irrational use of azithromycin and thereby reduce emerging resistance problems.[30]

SAFETY ISSUES ON THE USE OF AZITHROMYCIN

There are various side effects related to azithromycin. Precautions should be observed in all clinical cases.

The National Institutes of Health COVID-19 Treatment Guidelines state that the combination of HCQ and azithromycin was associated with QT prolongation in patients with COVID-19.[13] Likewise, the PSMID CPG states the same.[14] In year 2012, a research looked into the cardiovascular adverse effects of azithromycin. A Tennessee study demonstrated that azithromycin was associated with increased risk of death compared with amoxicillin (odds ratio 2.49, 95% CI 1.38-4.50).[15] A year later, a study published in New England Journal of Medicine (NEJM), found no increased risk of cardiac death among patients who took azithromycin relative to penicillin (rate ratio 0.93, 95% CI 0.56-1.55).[16] The 2012 Tennessee study demonstrated prolongation of QT interval, which is a major risk factor for torsades de pointes. The latter is a lethal arrhythmia that is associated with macrolides in general, and terfenadine, cisapride, astemizole, and grepafloxacin. Compared with

other macrolides, the occurrence of torsades de pointes is very rare, and this complication is more common among patients with other risk factors.[17]

A meta-analysis of 6 trials in which azithromycin was compared with placebo was conducted among 14,000 patients with known coronary disease demonstrated that azithromycin was associated with a trend toward decreased mortality (OR 0.91, 95% CI 0.77-1.09).[18] A more recent observational analysis with more than 70,000 adult patients with pneumonia found a lower mortality and no increase in arrhythmia in 90 days.[19] From these studies, it was shown that there are conflicting reports about the cardiovascular profile of this antibiotic. Some have concluded that the association with mortality most likely represents the effects of the infectious condition and not the side effects of azithromycin. The reported adverse cardiac complications are higher among patients with known and existing cardiovascular morbidity. But caution is observed when giving this drug to patients with preexisting QT abnormalities or with risk factors for it, especially those with hypokalemia, hypomagnesemia, and concomitant intake of other medicines, which could also cause QT prolongation.[20]

Adverse reactions include gastrointestinal effects such as diarrhea, nausea, and vomiting, which occur in about >10% of patients given this drug. Dermatologic effects are diaphoresis, eczema, fungal dermatitis, pruritus, and vesiculobullous dermatitis, especially among children (1-2%). Among adult, dermatologic manifestations (<1%) are skin photosensitivity, rash, and urticaria. Endocrine and metabolic side effects are decreased serum glucose, increased gamma-glutamyl transferase, increased lactate dehydrogenase, increased serum glucose, and increased potassium (1-3%). Genitourinary effects include candidiasis and vaginitis among adults (1-3%). Hematologic effects (1%) are anemia, eosinophilia, increased neutrophil count, leukopenia, lymphocytopenia, lymphocytosis, thrombocythemia, and monocytosis. Hypersensitivity reactions are rare (<1%) and may manifest as angioedema and true hypersensitivity reaction. Nervous system effects (<1%) include agitation, dizziness, fatigue, headache, insomnia, malaise, and vertigo. Nephrotoxic effects (1-3%) may be increased BUN levels, increased serum creatinine, and nephritis. Contraindications are known hypersensitivity to azithromycin, erythromycin, and other macrolides or to any of the components of the formulation. It is also not given to those with history of cholestatic jaundice, or hepatic disease experienced with a previous use of this antibiotic.[21]

Warnings and precautions include those related to the above-mentioned adverse effects especially cardiac effects, disease-related concerns such as when it is used to treat syphilis or gonorrhea because the drug may delay symptoms of incubating gonorrhea or syphilis. Concerns also include hepatic dysfunction in particular among those with preexisting liver conditions, and also among those inflicted with myasthenia gravis due to possible exacerbation. Precautions should also be

observed among patients with renal disease especially those with filtration rate <10ml/minute.[22]

SAFETY OF AZITHROMYCIN IN PREGNANCY

Azithromycin is relatively safe for use among pregnant women.

Azithromycin is classified under US FDA Class B. In a study about 123 pregnancy outcomes after exposure to azithromycin in 2006, 3 groups of women were enrolled: women who took the drug, women exposed to non-teratogenic antibiotics for the same conditions, and women exposed to non-teratogenic agents. Results showed that there were no significant differences in the 3 groups regarding the rate of congenital defects. The authors concluded that gestational exposure to this antibiotic is not associated with congenital malformation above the 1-3% rate in the general population. They concluded that azithromycin is safe for use in pregnancy.[23]

In a retrospective study published in 2013 by the American Society for Microbiology (ASM) entitled Fetal Safety of Macrolides, the authors investigated the occurrence of minor and major birth defects among pregnant women who used macrolides such as erythromycin, clarithromycin, azithromycin, and roxithromycin during the first trimester or the third trimester of pregnancy. They excluded chromosomal diseases and included about 105,492 births and 1,112 pregnancy terminations for 10 years between 1999 to 2009. Of these, about 1,033 fetuses were exposed to any of the antibiotics mentioned. Results showed that about 1,033 women were exposed to macrolides in the 1st trimester and there was no associated major or specific congenital abnormality accounting for maternal age, parity, ethnic origin, diabetes mellitus, and year of exposure (OR 1.08, 95% CI 0.84 to 1.38). And during the 3rd trimester about 959 women had use of macrolides. There was also no relationship between macrolide use and perinatal mortality, low birth weight, low APGAR score, or preterm birth. There was also no relation with pyloric stenosis or intussusception. The authors reported that macrolide use, including azithromycin intake, in the 1st trimester is not linked with increased incidence of major congenital defects. Likewise, use of this group of antibiotics is not also related to neonatal pyloric stenosis, or intussusception.[24]

In view of the above-cited studies and considering that azithromycin belongs to USFDA Pregnancy Category B, this macrolide is relatively safe for use among pregnant women. ***But given the results of the COALITION II trial, it was proven that adding azithromycin to any regimen for severe COVID does not produce beneficial results.***[30]

SAFETY OF AZITHROMYCIN IN BREASTFEEDING

Azithromycin can be given to lactating mothers with minimal to no risk for the neonate.

This drug is excreted in breast milk. After intake of 2 grams of azithromycin as a single dose to twenty women undergoing labor, the drug was present for up to 28 days in breast milk. There were no associated adverse effects on the breastfed babies.[25]

In another study, a lactating woman was given oral azithromycin for cellulitis, at 1 g loading dose followed by oral azithromycin at 500 mg for next 3 days. The concentration of azithromycin increased over time in her breast milk that reached a peak at 30th hour after the last dose.[26] Another study showed the mean half-life in breastmilk was about 15.6 hours but that the breast milk concentration was very low.[27]

In 2009, a prospective, controlled observational study on safety of macrolides during lactation was conducted among 55 infants exposed to macrolide antibiotics compared to 36 infants exposed to amoxicillin by breast feeding. The study revealed that the rates and types of minor adverse reactions among both groups of infants were comparable. They concluded that macrolide use by lactating women was not associated with pyloric stenosis, but the authors recommended to conduct further larger studies to confirm their observation.[28] From the manufacturer's stand, they recommend to consider risk of infant exposure when using macrolides to breastfeeding mothers.

From the US Centers for Disease Control and Prevention of Sexually Transmitted Diseases Treatment Guidelines, the authors state that azithromycin is one of recommended agents for the therapy of granuloma inguinale among lactating women. Additionally, this antibiotic is also considered an alternate agent among breastfeeding women suffering from lymphogranuloma venereum.[29]

Based on the above studies and recommendations from different authors, azithromycin can be given to lactating mothers with minimal to no risk for the neonate.

DOSAGE OF AZITHROMYCIN FOR THE TREATMENT OF COVID-19

Azithromycin is given as 500 mg on day 1, followed by 250 mg once a day for the next 4 days.

Azithromycin is always given together with hydroxychloroquine (HCQ). One case series used azithromycin at 500mg at day 1 followed by 250 mg daily for the next 4 days. A prospective study in France also used the same dosage. As was mentioned in the studies cited above, there are conflicting results of combination HCQ plus azithromycin. Until further studies or research will prove the utility of azithromycin in the therapy of coronavirus infection, there are no definite recommendations unless this drug is given in circumstances wherein the physician believes there would be more benefits than harm to the patient.

Given the results of the COALITION II trial, it was proven that adding azithromycin to any regimen for severe COVID does not produce beneficial results.[30]

Recommendation Number 3 from the PSMID-PCCP-PCP-PRA-PCHTM Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection, states that CQ or HCQ as monotherapy or in combination with a macrolide (e.g. azithromycin) or an antiviral agent (lopinavir-ritonavir, favipiravir) among hospitalized patients with probable or confirmed COVID-19 pneumonia is NOT recommended.[31]

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XVI. CHLOROQUINE AND HYDROCHLOROQUINE

Chloroquine (CQ) and hydroxychloroquine (HCQ) are immunomodulators developed more than 70 years ago. Both CQ and HCQ are used in rheumatology for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Both drugs inhibit cytokine production and modulate immune response through action on lysosomal activity and autophagy, effects on cell membrane stability and alterations in signaling pathways and transcriptional activity.[1]

During the early phase of the pandemic, the immunomodulatory effects of both drugs posed a theoretical clinical benefit especially in the control of the cytokine storm complicating COVID-19 infection. On March 28, 2020, the US FDA permitted the emergency use of HCQ and CQ for the treatment of adults or adolescents weighing 50 kg or more, hospitalized with COVID-19. Subsequently, on April 13, 2020, assessment as to the risk of cardiotoxicity of HCQ or CQ with or without azithromycin for COVID-19 treatment was undertaken. HCQ and CQ are associated with serious cardiac events particularly arrhythmias (prolongation of the QT interval). In a pharmacovigilance memorandum released by the US FDA dated May 19, 2020, involving 385 patients who used either HCQ or CQ for COVID-19, 109 patients reported serious cardiac adverse events such as QT prolongation, Torsades de Pointes, ventricular arrhythmia, ventricular tachycardia or ventricular fibrillation. Twenty-five (23%) of those who had serious cardiac adverse events had a fatal outcome. Serious non-cardiac adverse events were identified in 113 patients. Non-cardiac adverse events included hepatitis or increased liver enzymes or hyperbilirubinemia, acute kidney injury or renal failure, and methemoglobinemia.[2]

The Recovery (Randomized Evaluation of COVID-19 Therapy) Collaborative Group published their findings in the New England Journal of Medicine in October 8, 2020. The study was a randomized, controlled, open-label, platform trial involving 1,561 patients assigned to either a hydroxychloroquine arm or the usual care arm. The enrollment of patients was prematurely terminated on June 5, 2020 when an interim analysis determined a lack of efficacy for HCQ. Death within 28 days for the HCQ arm was seen in 27.0% of patients while death within 28 days in the usual care arm was 25.0% (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P= 0.15). The conclusion of the trial was that the HCQ arm did not have a lower incidence of death at 28 days compared to those who received usual care. [3]

HCQ was included in the WHO Solidarity Trial among other medications namely, remdesivir, lopinavir/ritonavir, and interferon-β1a. The HCQ and Lopinavir/Ritonavir arms of the trial were discontinued on June 20 and July 4, 2020, respectively. [4]

In light of new data, the use of CQ nor HCQ for the treatment or prophylaxis for COVID-19 infection is no longer recommended.

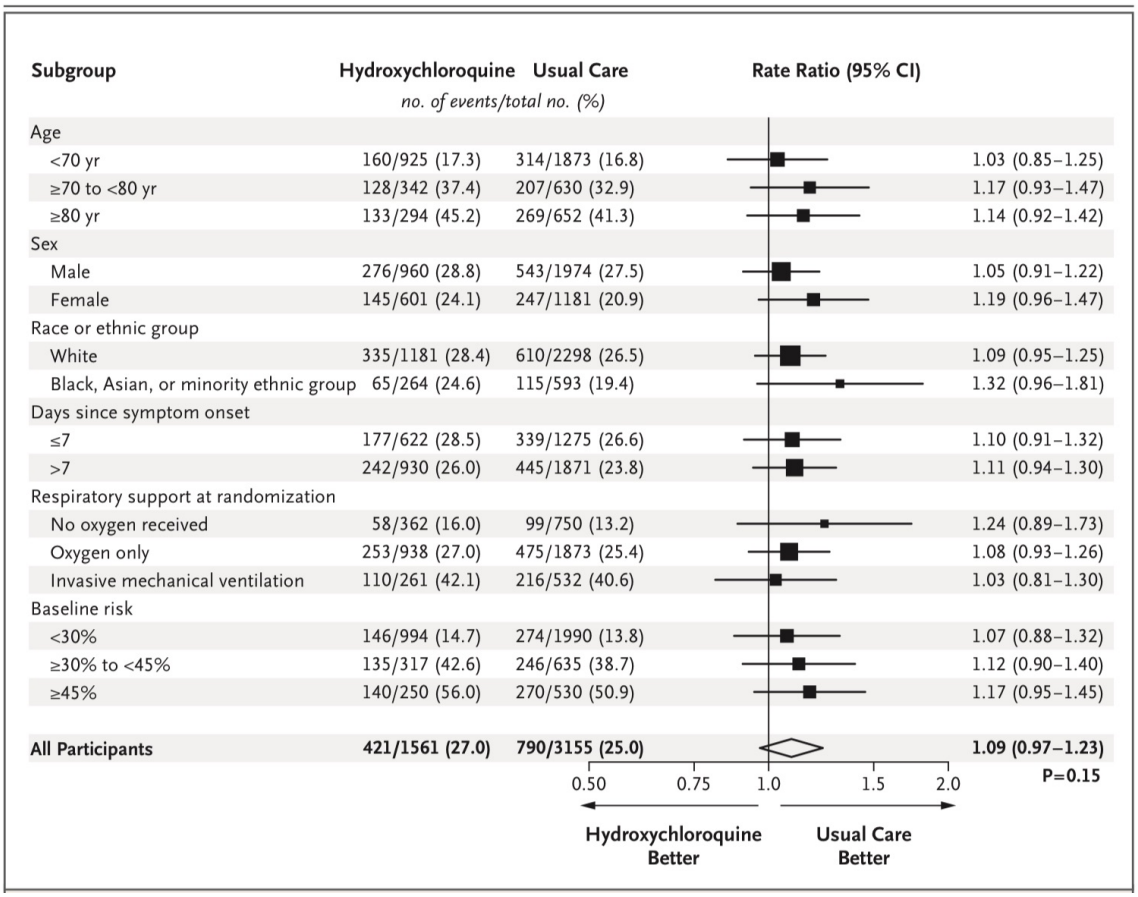

Figure 4.3 Mortality at 28 days, according to subgroup[3]

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WHAT ARE THE VACCINES BEING DEVELOPED AGAINST SARS-COV-2?

STATEMENT:

There are several vaccines under development in many countries. These vaccines are still undergoing clinical trials.

SUPPORTING STATEMENTS:

More than 150 vaccines against COVID-19 are in development across the world, including US, UK, Germany, India, China, Russia, and South Korea. More than 15 of the vaccines have started being tested in people. The vaccine trials are being conducted by Moderna, Pfizer and BioNTech, The University of Oxford and Astra Zeneca, Inovio, Johnson & Johnson, Bharat BioTech, Clover Bio Pharmaceuticals, CanSino, SinoPharm, Sinovac BioTech, Imperial College London and Morningside, Anges and Osaka University, Curevac, Genexine, Gamaleya Research Institute, Vaxine, Medicago, and the University of Queensland, among others. More vaccine candidates are likely to start clinical trials soon.

As of October 13, 2020, 4 vaccines have begun large-scale (Phase III) clinical trials in the US (i.e. Moderna, Pfizer and BioNTech, The University of Oxford and Astra Zeneca, and Johnson & Johnson). The US government's Operation Warp Speed Initiative aims to deliver 300 million doses of a safe, effective coronavirus vaccine by January 2021. The WHO, on the other hand, is eyeing delivery of 2 billion doses by the end of 2021.

Types of Vaccine: Several approaches to COVID-19 vaccines are currently being tested. They include both tried-and-true as well as novel approaches.

- **Inactivated vaccine** — The whole virus is killed with a chemical and used to make the vaccine (ex. inactivated polio, hepatitis A and rabies vaccines)

- **Subunit vaccine** — A piece of the virus that is important for immunity, like the spike protein of COVID-19, is used to make the vaccine (ex. hepatitis and HPV vaccines).

- **Weakened, live viral vaccine** — The virus is grown in the lab in cells different from those it infects in people. As the virus gets better at growing in the lab, it becomes less capable of reproducing in people. The weakened virus is then used to make the vaccine. When the weakened virus is given to people, it can reproduce enough to generate an immune response, but not enough to make the person sick (ex. measles, mumps, rubella, chickenpox and one of the rotavirus vaccines).

- **Replicating viral vector vaccine** — Scientists take a virus that doesn't cause disease in people (called a vector virus) and add a gene that codes

for, in this case, the coronavirus spike protein. Genes are blueprints that tell cells how to make proteins. The spike protein of COVID-19 is important because it attaches the virus to cells. When the vaccine is given, the vector virus reproduces in cells and the immune system makes antibodies against its proteins, which now includes the COVID-19 spike protein. As a result, the antibodies directed against the spike protein will prevent COVID-19 from binding to cells, and, therefore, prevent infection (ex. Ebola virus vaccine).

- **Non-replicating viral vector vaccine** — Similar to replicating viral vector vaccines, a gene is inserted into a vector virus, but the vector virus does not reproduce in the vaccine recipient. Although the virus can't make all of the proteins it needs to reproduce itself, it can make some proteins, including the COVID-19 spike protein. No currently licensed vaccines use this approach.

- **DNA vaccine** — The gene that codes for the COVID-19 spike protein is inserted into a small, circular piece of DNA, called a plasmid. The plasmids are then injected as the vaccine. No currently licensed vaccines use this approach.

- **mRNA vaccine** — The vaccine contains messenger RNA. mRNA is processed in cells to make proteins. Once the proteins are produced, the immune system will make a response against them to create immunity. In this case, the protein produced is the COVID-19 spike protein. No currently licensed vaccines use this approach.

It is likely that more than one of these approaches will work. The different approaches may have different strengths and weaknesses. For example, mRNA or DNA vaccines are much faster to produce, but neither has been used to successfully make a vaccine that has been used in people. On the other hand, killed viral vaccines and live, weakened viral vaccines have been used in people safely and effectively for many years, but they take longer to produce. Each type may also cause the immune system to respond differently. Understanding the immune responses that are generated will be important for determining whether additional (booster) doses will be needed, how long vaccine recipients will be protected, and if one type offers benefits over another.

Dosage: All but one of the COVID-19 vaccines currently in Phase III clinical trials in the US use 2 shots (1-2 months apart). The other vaccine uses 1 shot.

Eligible population: The Advisory Committee on Immunization Practices (ACIP), a committee within the United States Centers for Disease Control and Prevention (CDC), is considering 4 groups to possibly recommend COVID-19 vaccination if supply is limited:

1) Health care personnel
2) Workers in essential and critical industries
3) People at high risk for severe COVID-19 disease due to underlying medical conditions, and
4) People 65 years old and above.

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Recommended PPE Use for Healthcare Workers Caring for Suspected and Confirmed COVID-19 Pregnant Women

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WHAT IS PERSONAL PROTECTIVE EQUIPMENT?

Personal protective equipment, commonly referred to as PPE, is an equipment worn to minimize exposure and to stop the spread of COVID-19. It is one crucial way of keeping the frontliners safe.

WHAT CAN BE DONE TO ENSURE PROPER USE OF PERSONAL PROTECTIVE EQUIPMENT?

All personal protective equipment should be safely designed and made in a reliable fashion. It should fit comfortably, encouraging worker usage. If the personal protective equipment does not fit properly, it can make the difference between being safely covered or dangerously exposed. The things to consider when using PPEs are:

- What kind is necessary
- How to properly put it on, adjust, wear and take it off
- The limitations of the equipment
- Proper care, maintenance, useful life, and disposal of the equipment

WHAT ARE THE COMPONENTS OF PPE?

The components of PPE used when caring for suspected or confirmed COVID-19 pregnant patients will vary according to the setting and activity. Obstetrician-Gynecologists involved in the direct care of patients should use the following PPE:

1. **Disposable cap** – acts as a barrier to prevent microorganisms that may emerge from the hair and cause infection or contamination
2. **Eye goggles or Face shield** – prevents contamination to the eyes from splashing of secretions (including respiratory secretions), blood, body fluids or excretions
3. **Face mask** – prevents contamination from inhalation of respiratory secretions especially during an aerosol-generating procedure (Appendix E1 and E2)

a. ***Surgical mask / medical mask*** – filters out large particles in the air, protect through reducing exposure to the saliva and respiratory secretions
b. ***N95 mask*** – a type of respirator that offers more protection and can filter out both large and small particles. It is designed to block 95% of very small particles
c. ***FFP (Filtering Face Piece) mask*** – a half-face mask that protects the chin, nose and mouth; serves to protect against particulates such as dust particles and viruses
    - FFP1 – has the least filtering capacity
    - FFP2 – protection from powdered chemicals; can also serve as protection against several viruses and bacteria, similar to the N95 mask
    - FFP3 – has the most filtering capacity among the FFP masks; can protect against very fine particles
d. ***Elastomeric respirators*** – widely used by workers for industrial, mining, and military purposes, but they are not currently used widely in health care
e. ***Powered air-purifying respirator (PAPR)*** – used for protection during healthcare procedures in which there is a greater risk of aerosolized pathogens causing acute respiratory infections, its assigned protection factor exceed the APF of 10 for N95 FFR or elastomeric half face piece respirators

4. **Scrub suit** – sanitary clothing worn by the healthcare worker in the sterile environment
5. **Isolation or Disposable gown** – protects the clothes from contamination when providing direct patient care
6. **Coveralls / Disposable apron** – protective body wear that is fluid resistant to prevent the possibility of infected body fluids penetrating and contaminating the underlying clothes or skin with possible subsequent unrecognized transmission via the hands to the mucous membranes of the eyes, nose or mouth
7. **Disposable Gloves** – worn when providing direct patient care and to protect from exposure to blood and/or other body fluids.
8. **Footwear / Shoe covers** – helps maintain a sterile environment and eliminates the risk of contamination to the wearer

REFERENCES:

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WHAT ARE THE LEVELS OF PPE FOR HEALTHCARE WORKERS PROVIDING SERVICES TO PATIENTS?

STATEMENT:

There are recommended PPEs to minimize risk of cross-transmission of infection to self and others when providing patient care. The level of PPE that must be used by a healthcare worker is based on the identified or suspected infectious agent, severity of illness, route of transmission of infectious agent, area of care and anticipated exposure to blood or body fluids in the procedures undertaken.

SUPPORTING STATEMENTS:

Currently, an international and a local recommendation for PPE level use may be utilized. The Health Protection Scotland PPE has based their PPE level recommendation on the suspected or identified infectious agent being handled and the clinical scenario of anticipated risk which depends on route of microbial transmission, i.e. contact, droplet or airborne (Table 5-1). The local recommendation was devised by the Philippine General Hospital-Hospital Infection Control Unit (PGH-HICU) as part of its preparation for the establishment of PGH as a COVID center in the National Capital Region (NCR). Its recommendation is based on anticipated exposure risks from different areas in the hospital (Table 5-2, Appendix F). The PGH recommendation appears to be more apt for use in our local setting. However, clinicians should observe caution, possess good judgment and make sound decisions on what level of PPE to utilize based on anticipated risks in their geographic healthcare settings.

Table 5-1. Levels of Personal Protective Equipment according to Health Protection Scotland *

LEVEL	RECOMMENDED PPE	CLINICAL SCENARIO / INFECTIOUS AGENT
LEVEL 1 SICPs	**STANDARD INFECTION CONTROL PRECAUTIONS (SICPs)** • Disposable apron • Disposable gloves *If with risk of spraying or splashing, use eye and face protection (i.e. fluid-resistant Type IIR surgical face mask & full face visor or goggles)*	• No suspected or known infectious agent • Anticipated exposure to blood and/or other body fluids

LEVEL 2 CONTACT	**DIRECT / INDIRECT CONTACT PRECAUTIONS** • Disposable apron; consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure/task being performed • Disposable gloves *If with risk of spraying or splashing, use eye and face protection (i.e. fluid-resistant Type IIR surgical face mask & full face visor or goggles)*	• Suspected or confirmed infectious agent spread by direct/indirect contact: Examples: *C. difficile*, Hepatitis C, MRSA, *Salmonella* • Anticipated exposure to blood and/or other body fluids
LEVEL 2 DROPLET	**DROPLET (RESPIRATORY) PRECAUTIONS** • Disposable apron; consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure/task being performed • Disposable gloves • Fluid-resistant Type IIR surgical face mask & goggles or fluid-resistant Type IIR surgical face mask & full face visor	Suspected or confirmed infectious agent spread by the droplet route Examples: SARS-CoV-2, whooping cough, influenza
LEVEL 2 AIRBORNE	**AIRBORNE (RESPIRATORY) PRECAUTIONS** • Disposable apron; consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure/task being performed • Disposable gloves • Filtering face piece 3 (FFP3) respirator and eye protection or a powered hood respirator	Suspected or confirmed infectious agent spread by the airborne route Examples: Chickenpox, PTB, measles, SARS-CoV-2 (in aerosolizing procedures)
FOR **ALL AEROSOL-GENERATING PROCEDURES**: FFP3 respirator (and eye protection) or a powered hood respirator		

LEVEL	RECOMMENDED PPE	CLINICAL SCENARIO / INFECTIOUS AGENT
LEVEL 3 ENHANCED	**ENHANCED PRECAUTIONS** • Reinforced fluid-resistant long-sleeved surgical gown • Disposable fluid-resistant hood (if wearing a gown w/o an attached hood) • Full length disposable plastic apron • FFP3 respirator or powered hood respirator • Disposable full face visor • 2 sets of long or extended cuff non-sterile, non-latex disposable gloves • Surgical wellington boots or closed shoes • Disposable boot covers	For suspected or confirmed Infectious Diseases of High Consequence (IDHC) • Spread by DIRECT/INDIRECT CONTACT Examples: Ebola virus, Lassa virus • Spread by AIRBORNE ROUTE Examples: SARS, MERS-CoV, Avian Influenza, SARS-CoV-2 (aerosolizing procedures)

** Adapted from Public Health England & NHS Sheffield (Feb 2019)[1]*

Table 5-2. PGH-HICU Risk-Based Personal Protective Equipment Levels *

PPE LEVEL	PPE COMPONENTS	AREA (Based on PGH set-up)
LEVEL 1	• Surgical mask AT ALL TIMES • Alcohol plus hand hygiene	Non-COVID-19 Lowest Risk Areas
LEVEL 2	• Surgical mask AT ALL TIMES • Goggles/Face shield • Alcohol plus hand hygiene	Non-COVID-19 Low Risk Areas

LEVEL 3	• N95, KN95, FPP2 mask (fit-tested) • Goggles/Face shield • Surgical cap • Double gloves • Surgical gown • Scrub suits • Shoe covers	COVID-19 Moderate Risk Areas • In COVID areas where stay is < 4hrs • During brief interaction with patients • To perform NPS/OPS swab • For all safety officers in the doffing areas • COVID-19 Triage Area • Areas with suspect COVID-19 cases
LEVEL 4	• N95 mask (fit-tested) • Goggles/Face shield (covers front and sides of face with no areas left uncovered) • Surgical cap • Double gloves • Coveralls • Scrub suits • Dedicated shoes • Shoe covers	COVID-19 High Risk Areas • In COVID areas where stay is > 4 hours • When performing close contact with patients (intubation, doing CPR, suctioning ET, inserting NGT, changing linens/diaper) • In the OR theater during procedures or surgery • At the ER to evaluate or stabilize new patients with unknown status ***In case of doubt if Level 3 or 4, opt for Level 4 PPE***

** Adapted from PGH HICU Risk-based PPE Levels "What to Wear" (April 24, 2020)*

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2. Recommendations from PGH HICU PPE LEVELS infographic on "What to Wear". March 29,2020.
3. Recommendations from PGH HICU PPE LEVELS Infographic on "What to Wear". April 24,2020.

WHAT ARE THE RECOMMENDED LEVELS OF PPE AS TO HEALTHCARE TASK AND AREAS OF EXPOSURE IN THE HOSPITAL?

STATEMENT:

The PPE is essential in protecting healthcare workers from infectious agents transmitted through contact, droplet or by airborne route.[1] To streamline this process, the recommended level of PPE is classified according to healthcare personnel task and area of exposure in the hospital (Table 5.3).[2,3]

Table 5-3. Levels of PPE According to Task and Area of Exposure

AREA 1: PATIENT IN SCREENING ZONE			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
Doctors and nurses	Triage stable suspect case of COVID-19	• Disposable gloves • Apron (disposable and water repellant) *Consider fluid-resistant disposable gown if apron is inadequate to provide protection for the procedure/task being performed*	LEVEL 2 (Contact)
Doctors and nurses	Initial evaluation of unstable suspect case of COVID-19 at triage area	• Disposable gloves • Apron (disposable and water repellant) • Surgical face mask and goggles OR surgical face mask and full-face visor	LEVEL 2 (Contact, Droplet)
AREA 2: PATIENT IN TRANSIT TO TREATMENT ZONE, DELIVERY ROOM OR OPERATING ROOM COMPLEX (AMBULANCE OR STRETCHER-BORNE)			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
Paramedics Ambulance Driver Utility Worker	Transport and carry suspect, probable or confirmed COVID-19 pregnant patients	• Disposable gloves • Apron, disposable and water repellant • Surgical face mask and goggles OR surgical face mask and full-face visor	LEVEL 2 (Contact, Droplet)

AREA 2: PATIENT IN TRANSIT TO TREATMENT ZONE, DELIVERY ROOM OR OPERATING ROOM COMPLEX (AMBULANCE OR STRETCHER-BORNE)			
Utility Worker Janitorial	Disinfection of the ambulance	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Scrub suit • Disposable gown • Shoe covers	LEVEL 3
AREA 3: PATIENT IN TREATMENT ZONE			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
ICU/NICU (HIGH RISK)			
Doctors and nurses	Management of suspect, probable or confirmed COVID-19 pregnant patient	• 2 sets of disposable gloves, long or extended cuff, non-sterile, non-latex • Apron, full length disposable and water repellant • Surgical gown, long sleeved and fluid resistant • Filtering facepiece 3 (FFP3) respirator or a powered hood respirator • Disposable fluid resistant hood (if wearing a gown without an attached hood) • Disposable full visor/face shield • Surgical wellington boots/closed shoes • Disposable boot covers	LEVEL 3 (Enhanced)

AREA 3: PATIENT IN TREATMENT ZONE			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
WARD			
Doctors and nurses	Management of suspect, probable or confirmed COVID-19 postpartum patients	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Disposable gown or impermeable coveralls • Shoe covers	LEVEL 3
	Performing CPR	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Scrub suit • Coveralls • Dedicated shoes • Shoe covers	LEVEL 4
LABOR ROOM / DELIVERY ROOM / OPERATING ROOM			
Doctors and nurses	Labor and delivery of suspect, probable or confirmed COVID-19 pregnant patient	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Scrub suit • Coveralls • Dedicated shoes • Shoe covers	LEVEL 4
Utility Workers Cleaners	Labor and delivery of suspect, probable or confirmed COVID-19 pregnant patient	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Scrub suit • Disposable gown • Shoe covers	LEVEL 3

AREA 3: PATIENT IN TREATMENT ZONE			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
OUTPATIENT CLINIC AND ULTRASOUND UNIT			
Physicians Sonologist Nurses Utility Workers Cleaners	Consultation room Ultrasound room Performing diagnostic tests	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Disposable gown or impermeable coveralls • Shoe covers	LEVEL 3
AREA 4: NON-TREATMENT HOSPITAL ZONES / AREAS			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
Accounting Billing Cashier	Receive cash or paper money payments	• Disposable gloves • Apron, disposable and water repellant • Surgical face mask and goggles OR surgical face mask and full-face visor	LEVEL 1
HR / IT / Medical records	Heavy handlers of papers or surfaces	• Surgical facemask AT ALL TIMES • Alcohol/Hand hygiene	LEVEL 1
Kitchen Mess Hall	Food handlers in direct contact with exposed personnel	• Surgical facemask AT ALL TIMES • Alcohol/Hand hygiene	LEVEL 1
Pharmacy	Issue medicines and supplies	• Surgical facemask AT ALL TIMES • Alcohol/Hand hygiene	LEVEL 1

AREA 4: NON-TREATMENT HOSPITAL ZONES / AREAS			
HEALTH PERSONNEL	**TASK**	**PPE**	**RECOMMENDED LEVEL OF PPE**
Executive offices	Indirect contact with suspect, probable and confirmed COVID-19 patient	• Surgical facemask AT ALL TIMES • Alcohol/Hand hygiene	LEVEL 1
Hospital support group and Janitorial services	Clean patient's bathrooms Disinfect rooms of probable, suspect or confirmed COVID-19 patient	• N95 Mask • Goggles/Face shield • Surgical cap • Double gloves • Scrub suit • Disposable gown • Shoe covers	LEVEL 3

REFERENCES:

1. Aide Memoire for Levels of Personal Protective Equipment (PPE) – NIPCM. Appendix 16. http://www.nipcm.hps.scot.nhs.uk/appendices/appendix-16-best-practice-aide-memoire-for-levels-of-personal-protective-equipment-ppe-for-healthcare-workers-when-providing-patient-care/. V1.0 February 20
2. Recommendations from PSMID Article on "Interim Guidelines on the Infection Prevention and Control (IPC) for COVID-19: Suggested PPEs According to Tasks (Table 2)" V 2.0. pp 9-10. February 26, 2020.
3. Recommendations from PGH HICU PPE LEVELS infographic on "What to Wear". March 29,2020.
4. Recommendations from PGH HICU PPE LEVELS Infographic on "What to Wear". April 24,2020.

WHAT IS THE RECOMMENDED PPE LEVEL TO BE USED DURING OBSTETRIC AND GYNECOLOGIC PROCEDURES?

STATEMENT:

For COVID-19 suspect and confirmed pregnant patients, healthcare providers should use the level 3 personal protective equipment (PPE) for all minor procedures and in performance of moderate-risk activities, and level 4 PPE for major procedures.

SUPPORTING STATEMENTS:

A level 3 PPE is enhanced precaution and consists of the following: cap, goggles or face shield, N95 mask, double gloves, scrub suits, surgical gown and shoe covers (Appendix G-1 and G-2).

A level 4 PPE is level 3 (i.e. cap, goggles or face shield, N95 mask, double gloves, scrub suits and shoe covers), with the addition of the following components for added protection: surgical cap, coveralls, sterile surgical gown, sterile gloves, apron/raincoat (optional) and dedicated shoes (Appendix H-1 to H3).

Table 5-4. Areas and activities involved where level 3 and level 4 PPEs are used

PPE Level	AREAS AND ACTIVITIES INVOLVED
LEVEL 3	1. At the COVID-designated areas staying < 4 hours 2. Doing history-taking, physical examination (doing pelvic or internal examination) 3. Performing chest x-ray, blood extraction, making daily rounds 4. Performing transvaginal / abdominal ultrasound 5. Performing nasopharyngeal and oropharyngeal specimen collection (NPS/OPS swabbing) 6. At the Doffing area - for safety officers
LEVEL 4	1. At the COVID-designated areas staying > 4 hours 2. Transferring the patient 3. Performing change of bed linens with the patient on the bed 4. Changing diapers and doing personal hygiene on the patient 5. Suctioning procedures 6. Doing oral or endotracheal care, insertion of nasogastric tube (NGT - use additional apron or raincoat) 7. Performing intubation and cardiopulmonary resuscitation (CPR - use additional apron or raincoat) 8. At the operation room theatre (OR), in the performance of any obstetrics and gynecologic surgery – don sterile surgical gown and sterile gloves 9. Stabilizing patients at the Emergency Room (ER)

REFERENCES:

1. Recommendations from PSMID Article on "Interim Guidelines on the Infection Prevention and Control (IPC) for COVID-19: Suggested PPEs According to Tasks (Table 2)" V 2.0. pp 9-10. February 26, 2020.2
2. Recommendations from PGH Article on "What Personnel Protective Equipment to Wear". March 29, 2020.

WHAT IS THE PROPER SEQUENCE OF DONNING AND DOFFING PPE IN OBSTETRIC AND GYNECOLOGIC PROCEDURES?

STATEMENT:

The type of PPE used will vary based on the level of precautions required. The procedure for donning and doffing of PPE should be tailored to the specific type of PPE.

SUPPORTING STATEMENTS:

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have guidelines on the proper donning and doffing of PPEs. More than one donning and doffing method may be acceptable. Training and demonstrated competency in donning and doffing PPE ensure proficiency in the use of the equipment.

DONNING METHOD USING LEVEL 3 PPE

1. Remove all personal items (ex. jewelry, watches, cellphones, etc.).
2. Put on scrub suit.
3. Identify and gather the proper PPE to don.
   - Make sure choice of gown size is correct (based on training)
   - Undertake the procedure of putting on PPE under the guidance and supervision of trained observer.
4. Perform hand hygiene.
5. Put on shoe covers.
6. Put on isolation gown.
   - Tie all of the ties on the gown.
   - Assistance may be needed by other healthcare personnel.
7. Put on NIOSH-approved N95 filtering facepiece respirator or higher (use facemask if respirator is not available).
   - If the respirator has a nosepiece, it should be fitted to the nose with both hands, not bent or tented. Do not pinch the nosepiece with one hand.
   - Respirator / facemask should be extended under the chin. Both your mouth and nose should be protected. Do not wear respirator / facemask under your chin or store in scrubs pocket between patients.
   - *Respirator:* Respirator straps should be placed on crown of head (top strap) and base of neck (bottom strap). Perform a user seal check each time you put on the respirator.
   - *Facemask:* mask ties should be secured on crown of head (top tie) and base of the neck (bottom tie). If mask has loops, hook them appropriately around your ears.
8. Put on the face shield or goggles.
   - Face shields provide full face coverage.

- Goggles also provide excellent protection for the eyes, but fogging is common.

9. Put on head cover or surgical cap.
10. Perform hand hygiene.
11. Put on pair of gloves.
    - Gloves should cover the cuff (wrist) of the gown.

DONNING METHOD USING LEVEL 4 PPE

1. Remove all personal items (ex. jewelry, watches, cellphone, pens, etc.)
2. Put on scrub suit and dedicated shoes/rubber boots and put on shoe cover.
    - If rubber boots are not available, make sure you have closed and fluid resistant shoes.
3. Identify and gather the proper PPE to don.
    - By visual inspection, ensure that all sizes of the PPE are correct, and the quality is appropriate.
    - Undertake the procedure of putting on the PPE under the guidance and supervision of a trained observer.
4. Perform hand hygiene.
5. Put on first pair of gloves.
6. Put on coverall.
    - Do not use adhesive tape to attach the gloves.
    - If the gloves or the coverall sleeves are not long enough, make a thumb (or middle finger) hole in the coverall sleeve to ensure that your forearm is not exposed when making wide movements.
    - Some coverall models have finger loops attached to sleeves.
7. Put on NIOSH-approved N95 filtering facepiece respirator or higher
    - Use facemask if respirator is not available
    - Perform a user seal check each time you put on the respirator
8. Put on face shields or goggles
9. Put on head and neck covering (surgical bonnet/cap, covering neck and sides of the head or hood).
10. Put on disposable waterproof apron (optional)
    - Apron that covers the torso and extends to mid-calf may be worn for additional protection in case a patient has diarrhea or is vomiting
11. Put on second pair of gloves (preferably long cuff) over the cuff.
    - Do not use adhesive tape to attach the gloves.
12. Put on sterile gown and sterile gloves without contamination if a sterile obstetric or gynecologic surgery is to be performed after doing hand hygiene.

DOFFING METHOD USING LEVEL 3 PPE

1. Always remove PPE under the guidance and supervision of a trained observer.
    - Ensure that infectious waste containers are available in the doffing area for safe disposal of PPE.
    - Separate containers should be available for reusable items
2. Perform hand hygiene on gloved hands.
3. Remove shoe covers by one gloved hand
4. Remove pair of gloves.
    - Ensure glove removal does not cause additional contamination of the hands. Gloves can be removed using more than one technique (e.g., glove-in-glove or bird beak)
5. Remove gown.
    - Untie all ties (or unsnap all buttons). Some gown ties can be broken rather than untied. Do so in gentle manner, avoiding forceful movement.
    - Reach up to the shoulders and carefully pull gown down and away from the body. Rolling the gown down is an acceptable approach.
    - Dispose in trash receptacle.
    - Facilities implementing the reuse or extended use of PPE will need to adjust their donning and doffing procedures to accommodate those practices
6. Perform hand hygiene.
7. Remove head cover or surgical cap.
8. Remove face shield or goggles.
    - Carefully remove face shield or goggles by grabbing the strap and pulling upwards and away from the head.
    - Do not touch the front of face shield or goggles.
9. Remove and discard respirator (or facemask if used instead of respirator).
    - Do not touch the front of the respirator or facemask.
    - Facilities implementing the reuse or extended use of PPE will need to adjust their donning and doffing procedures to accommodate those practices.
    - *Respirator:* Remove the bottom of the strap by touching only the strap and bring it carefully over the head, and then pull the respirator away from the face without touching the front of the respirator.
    - *Facemask:* Carefully untie (or unhook from the ears) and pull away from the face without touching the front.
10. Perform hand hygiene after removing the respirator/facemask and before putting it on again if your workplace is practicing reuse.

- Facilities implementing the reuse or extended use of PPE will need to adjust their donning and doffing procedures to accommodate those practices

DOFFING METHOD USING LEVEL 4 PPE

1. Always remove PPE under the guidance and supervision of a trained observer (colleague).
    - Ensure that infectious waste containers are available in the doffing area for safe disposal of PPE.
    - Separate containers should be available for reusable items.
2. Perform hand hygiene on gloved hands.
3. Remove apron (if worn) by leaning forward and taking care to avoid contaminating your hands.
    - When removing disposable apron, tear it off at the neck and roll it. Down without touching the front area. Then untie the back and roll the apron forward.
4. Remove shoe covers (if worn).
5. Perform hand hygiene on gloved hands.
6. Remove head and neck covering taking care to avoid contaminating your face by starting from the bottom of the hood in the back and rolling from the back to front and from the inside to outside, and then dispose of it safely.
7. Perform hand hygiene on gloved hands.
8. Remove coverall and outer pair of gloves.
    - Ideally this step should be done in front of a mirror.
    - Tilt head back to reach zipper, unzip completely without touching any skin or scrubs, and start removing coverall from top to bottom. After freeing shoulders, remove the outer gloves.
    - This procedure requires properly fitted gloves. When outer gloves are too tight or inner gloves are too loose and/or hands are sweaty, the outer gloves may need to be removed separately, after removing the apron while pulling the arms out of the sleeves. With inner gloves roll the coverall, from the waist down and from the inside of the coverall, down to the top of the boots. Use one boot and vice versa, then step away from the coverall and dispose of it safely.
9. Perform hand hygiene on gloved hands.
10. Remove eye protection (face shield and goggles) by pulling the string from behind the head and dispose of it safely.
11. Perform hand hygiene on gloved hands.
12. Remove the mask from behind the head by first untying the bottom string above the head and leaving it hanging in front; and then the top string next from behind head and dispose of it safely.
13. Perform hand hygiene on gloved hands.

- Remove the rubber boots without touching them
- If the same boots are to be used outside of the high-risk zone, keep them on but clean and decontaminate appropriately before leaving the doffing area.

14. Perform hand hygiene on gloved hands.
15. Remove gloves carefully with appropriate technique and dispose of them safely.
16. Perform hand hygiene.

REFERENCES:

1. Using Personal Protective Equipment. Accessed thru: https://www.cdc.gov
2. Steps to put on/take off personal protective equipment including coverall. Accessed thru: https://www.who.int

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF PPE GOWNS AND COVERALLS BASED ON TYPE OF MATERIAL USED?

STATEMENT:

Materials used for coverall and isolation gown for PPEs can be woven or non-woven fabric. Each has its advantages and disadvantages.

Table 5-5. Types of Material Used for Coveralls and Isolation Gowns

TYPE OF GOWN	MATERIAL	ADVANTAGES	DISADVANTAGES
Medical-grade coverall or gown	GSM fabric material (non-woven)	• Bacterial barrier • Water repellant • Washable • 90 days life span	• High susceptibility to UV degradation • Poorly-resistant to chlorinated solvents and aromatics[1]
Improvised coverall or gown	Taffeta cloth with 70 Denier Heat Sealable / Taslan (woven nylon or polyester)	• Washable • Waterproof • Reusable • Lightweight • Heat-resistant	• Porous • Non-biodegradable • May cause allergic reaction to resin component • Cannot be used if in direct contact with skin; body heat interacts with polyester component that release toxic chemicals and may be absorbed by the skin[1]

REFERENCES:

1. Antimicrobial Characteristics of Pulsed Laser Deposited Metal Oxides on Polypropylene Hydroentangled Nonwovens for Medical Textiles. https://www.researchgate.net/publication/316958768_Antimicrobial_Characteristics_of_Pulsed_Laser_Deposited_Metal_Oxides_on_Polypropylene_Hydroentangled_Nonwovens_for_Medical_Textiles

WHAT ARE THE NON-WOVEN FABRIC MATERIALS USED IN PPEs?

STATEMENT:

Non-woven fabric materials are textiles made thru a process other than weaving. They are extruded or blown fibers, usually polyethylene and polypropylene, that are bound into fabric using heat, and finished to achieve repellence, absorbance and anti-static properties. The basic method of producing this material is by "spun-bonding". Other methods result in a different type of finished fabric (Table 5.5).[1]

Table 5-6. Non-Woven Fabric Materials Used for Standard Coverall and Improvised PPEs

TYPE OF FABRIC	DESCRIPTION	TYPE OF FIBER USED	NO. OF LAYERS
Flashspun Polyethylene (FSPE)	Dense structure of fine continuous polyethylene fibers	100% polyethylene fiber	1
Microporous Film Laminate (MPFL)	Microporous layer features interlinked cavities forming "wormholes" through the film	*Outer layer:* polyethylene fiber *Inner layer:* polypropylene fiber	2
Spun bond-Melt blown-Spun bond (SMS)	Spunbond layer provides strength Meltblown layer provides filtration	3 layers of propylene fibers	3

REFERENCES:
1. Coverall Standards@safegardGP.pdi.

IS THERE A STANDARD TESTING FOR FABRICS IN PROTECTING AGAINST INFECTIOUS AGENTS AND BIOLOGICAL HAZARDS?
STATEMENT: **Yes. The EN 14126 is the standard protective clothing against infectious agents and biological hazards. It defines no requirements for garment construction, but undergoes four different tests which measure a fabric's ability to resist penetration by liquids that may be contaminated by bacteria or other infectious agents.[1]**

Table 5-7. Fabric Testing for EN 14126 Infectious Agent Protection[2]

COMPARISON OF FLASHSPUN POLYETHYLENE (FSPE) AND MICROPOROUS FILM LAMINATE (MPFL)				
TEST DESCRIPTION	**TEST #**	**CLASSES**	**FPSE**	**MPFL**
Resistance to Penetration by Biological Contaminated Aerosols	ISO 22611	1 TO 3 (3=highest)	1	3
Resistance to Penetration by Blood-borne Pathogens	ISO 16604	1 TO 6 (6=highest)	unclassified	6
Resistance to Penetration by Contaminated Liquids	EN ISO 22610	1 TO 6 (6=highest)	1	6
Resistance to Contamination by Solid Particles	ISO 22612	1 TO 3 (3=highest)	1	3
*SMS fabric is not tested because it is not recommended for this type of protection.[2]				

REFERENCES:
1. Coverall Standards@safegardGP.pdi.
2. Lill, Martin. "Type 6 Disposable Safety Clothing: Which Coveralls Offer Best Liquid Protection?". Lakeland Europe Blog. August 30, 2019.

HOW ARE PPEs DISINFECTED FOR REUSE?

STATEMENT:

PPEs are intended to be disposed after a single use. However, the abrupt large-scale increase in demand during this pandemic has depleted the current global stockpile and manufacturers are unable to keep up with the worldwide request for supplies. For this reason, WHO released interim guidelines on the extended use and reprocessing of PPEs. The CDC also released strategies for effective decontamination which aim to sterilize the PPEs for reuse while maintaining their protective functions to the user.[1,2,3,]

Table 5-8. Sterilization and Disinfection Techniques for PPEs

PPE	METHOD OF DISINFECTION
FFP3 / N95 masks	Preserve the integrity of the mask by decontamination through use of: 1) vaporous hydrogen peroxide, 2) 6% liquid hydrogen peroxide submersion for 30 minutes, 3) UV germicidal irradiation or 4) moist heat at 60ºC and 85% RH (relative humidity) Avoid using isopropyl alcohol, soap, bleach, autoclave, dry heat and microwave for disinfection as they cause significant filter degradation and disruption of particle penetration level.[1] Limit number of reuses to no more than 5 times to ensure adequate safety margin.[2]
Goggles / Face shields and hoods	Clean with soap and water followed by disinfection using either sodium hypochlorite 0.1% (1:1000) or 70% alcohol wipes. Then rinse off with water. Contact time when using sodium hypochlorite disinfectant must be at least 10 minutes for optimum sterilization.[3]
Isolation gown / Cotton gowns	Machine-wash with warm water (60-90°C) and laundry detergent. If machine-washing is not possible, linen can be soaked in hot water and soap in a large drum, using a stick to stir, taking care to avoid splashing. Then soak linen in 0.05% chlorine for approximately 30 minutes. Rinse with clean water and let dry fully in the sunlight.[3]

REFERENCES:

1. CDC website on Coronavirus 2019: "Decontamination and Reuse of Filtering Facepiece Respirators". April 29, 2020.
2. CDC website on The National Institute for Occupational Safety and Health (NIOSH) Pandemic Planning: "Recommended Guidance for Extended Use and Limited Reuse of N95 Filtering Facepiece Respirators in Healthcare Settings". March 27,2020.
3. WHO Interim Guidance: "Rational use of PPE for coronavirus disease (COVID-19) and considerations during severe shortage". April 6, 2020.

WHAT ARE SOME OF THE INNOVATIONS CREATED TO PROTECT HEALTHCARE WORKERS DURING THIS COVID-19 PANDEMIC?

STATEMENT:

With the increasing incidence of healthcare workers getting infected with the COVID-19 while handling their patients here in our country, a number of novel improvised barriers were invented by colleagues in the medical field to address this concern. The main objective of which is to protect healthcare workers by minimizing their exposure to patients when necessary procedures or diagnostics need to be undertaken.

Table 5-9. Improvised Barrier Protection Against SARS-CoV-2 in Different Healthcare Settings

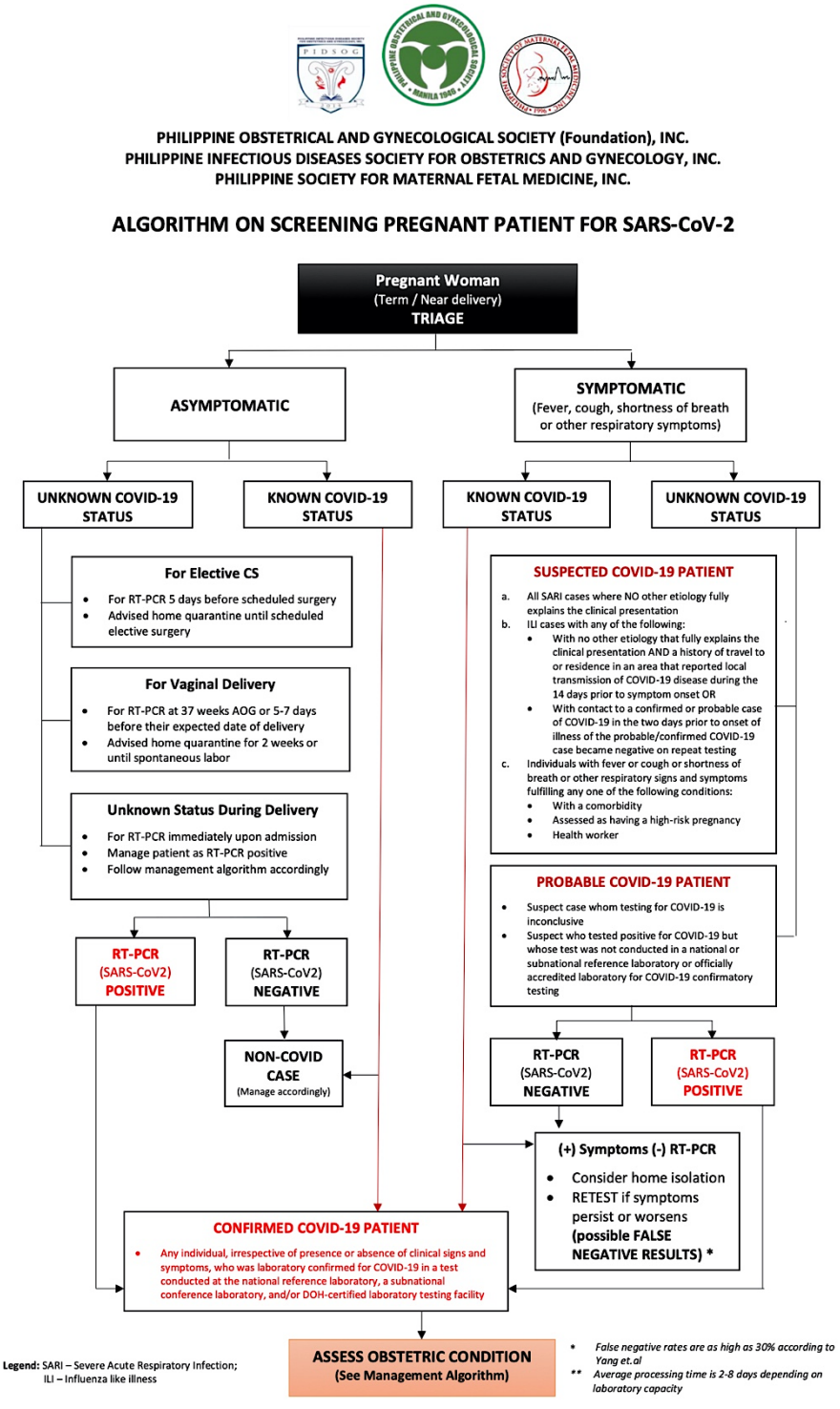
IMPROVISED BARRIER	USES	BENEFIT	HARM OR LIMITATION
Acrylic aerosol box	Endotracheal intubation	Minimizes exposure to droplets while performing intubation	Poor organ exposure due to limitation of mobility
	Consultation barrier	Minimizes exposure to droplets during history-taking	Limited protection Limited access to patient for doing physical examination
Plastic-covered isolation compartment	Labor/Delivery	Minimizes exposure to droplets/aerosols during second stage of labor and during delivery	Prolonged use can lead to suffocation
	Ultrasound procedures	Minimizes exposure to droplet for both sonologist and machine	Poor disinfection between patients may lead to enhancement of transmission

Table 5-10. Miscellaneous Agents Used Against SARS-CoV-2 for Protection of Healthcare Workers and/or their Environment

AGENT	USES	BENEFIT	HARM OR LIMITATION
Ultraviolet Germicidal Irradiation (UVGI)	Inactivates microorganisms by destruction of their nucleic acid through strand breakage and formation of photo-induced byproducts such as thymine dimer. Damaged nucleic acid cannot be used for cell reproduction.[1]	Destroys airborne organisms and inactivates microorganisms on surfaces[2] Suitable for viruses because of their higher susceptibility to UVGI than bacteria. Viruses are also difficult to filter because of their size.[1]	Can cause eye damage (cataract formation, macular degeneration) and surface burns on unshielded skin, eyes and other organs[1] Kills microorganisms depending on UV intensity and time of exposure.[1] Germicidal effectiveness and use is influenced by organic matter, temperature, wavelength and type of microorganism[2]
High Efficiency Particulate Air (HEPA) Filter	Captures a portion of airborne virus-sized particles by diffusion. Trapped viruses cannot multiply on their own[2] Newer models provide efficiency down to 0.1 micron particle size at a removal efficiency of 99.97%[1]	Effective at removing bacteria, fungus, some viruses and large particulate allergens like pollen, dander, and dust mites[3]	Molds and bacteria can grow on filters. Spores from molds can get released back into the air while endotoxins from degraded bacteria can get dispersed into the airstream.[3] Filters should be replaced regularly every 6 months for commercial use and up to 1-2 years for residential use.[3]

REFERENCES:
1. Schentagg, JJ et. al. . SARS: Clearing the Air. Washington DC: National Academics Press (USA). 2004.
2. www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-prevent-spread
3. "Pros and Cons of HEPA Filter Air Purifiers, Dissected" at https://molekule.science/pros

APPENDIX A: Algorithm on Screening Pregnant Patients for SARS-CoV-2



DISCLAIMER: ***This algorithm was formulated to guide clinicians on the benefit of SARS-CoV-2 testing in this population. This recommendation can be adopted and modified based on geographical risk, available resources and testing capacity of each institution or facility.***

APPENDIX B-1: Empiric Antimicrobial Therapy for Low-Risk Community Acquired Pneumonia with usual recommended dosages in 50-60kg adults with normal liver and renal functions

Risk Stratification	Potential Pathogens	Empiric Therapy
Low-risk CAP Stable VS: RR <30/min PR <125/min SBP > 90 mmHg DBP >60 mmHg Temp >36 °C or <40 °C • No altered mental state of acute onset • No suspected aspiration • No or stable co-morbid conditions • Chest X-ray - Localized infiltrates - No evidence of pleural effusion	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli (among those with co-morbid illness)	**Without co-morbid illness** Amoxicillin 1 gm TID OR Extended Macrolides Azithromycin 500mg OD OR Clarithromycin 500mg BID **With stable co-morbid illness** ß-lactam/ß-lactamase inhibitor combination (BLIC) OR 2nd Gen oral Cephalosporin +/- extended macrolides Co-amoxyclav 1 gm BID OR Sultamicillin 750 mg BID OR Cefuroxime axetil 500 mg BID +/- Azithromycin 500mg OD OR Clarithromycin 500mg BID

SOURCE: *Joint Statement of the Philippine Society for Microbiology and Infectious Diseases, Philippine College of Chest Physicians, Philippine Academy of Family Physicians, Inc. and Philippine College of Radiology. Philippine Clinical Practice Guidelines. Diagnosis, Empiric Management and Prevention of Community-Acquired Pneumonia in Immunocompetent Adults 2016 Update Treatment.*

APPENDIX B-2: Empiric Antimicrobial Therapy for Moderate-Risk Community Acquired Pneumonia with usual recommended dosages in 50-60kg adults with normal liver and renal functions

Risk Stratification	Potential Pathogens	Empiric Therapy
Moderate-risk CAP *Unstable VS:* RR ≥30/min PR ≥125/min SBP < 90 mmHg DBP <60 mmHg Temp ≤36 °C or ≥40 °C • Altered mental state of acute onset • Suspected aspiration • Unstable/Decompensated co-morbid condition - uncontrolled DM - active malignancies - neurologic disease in evolution - congestive heart failure (CHF) Class II-IV - unstable coronary artery disease - renal failure on dialysis - uncompensated COPD - decompensated liver disease	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli *Legionella pneumophilia* Anaerobes (among those with risk of aspiration)	IV non-antipseudomonal ß-lactam (BLIC, cephalosporin) + extended macrolides or respiratory fluoroquinolones (PO) Ampicillin-Sulbactam 1.5gm q6h IV OR Cefuroxime 1.5gm q8h IV OR Ceftriaxone 2gm OD + Azithromycin 500mg OD PO OR Clarithromycin 500mg BID PO OR Levofloxacin 500mg OD PO OR Moxifloxacin400mg OD PO
Moderate-risk CAP *Unstable VS:* RR ≥30/min PR ≥125/min SBP < 90 mmHg DBP <60 mmHg Temp ≤36 °C or ≥40 °C • Altered mental state of acute onset • Suspected aspiration • Unstable/Decompensated co-morbid condition - uncontrolled DM - active malignancies - neurologic disease in evolution - congestive heart failure (CHF) Class II-IV - unstable coronary artery disease - renal failure on dialysis - uncompensated COPD - decompensated liver disease	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* Enteric Gram-negative bacilli *Legionella pneumophilia* Anaerobes (among those with risk of aspiration)	If **aspiration pneumonia** is suspected and, a regimen containing Ampicillin-Sulbactam and/or Moxifloxacin is used, there is no need to add another antibiotic for additional anaerobic coverage. If another combination is used, may add Clindamycin to the regimen to cover microaerophilic streptococci Clindamycin 600mg q8h IV OR Ampicillin-Sulbactam 3gm q6h IV OR Moxifloxacin 400mg OD PO

APPENDIX B-3: Empiric Antimicrobial Therapy for High-Risk Community Acquired Pneumonia with usual recommended dosages in 50-60kg adults with normal liver and renal functions[1]

Risk Stratification	Potential Pathogens	Empiric Therapy
High-risk CAP Any of the clinical feature of **Moderate-risk CAP plus** any of the following: *Severe Sepsis and Septic Shock OR* *Need for Mechanical Ventilation*	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* *Enteric Gram-negative bacilli* *Legionella pneumophilia* *Anaerobes (among those with risk of aspiration)* *Staphylococcus aureus* *Pseudomonas aeruginosa*	***No risk for P. Aeruginosa*** IV non-antipseudomonal ß-lactam + IV extended macrolides or respiratory fluoroquinolones Ceftriaxone 2 gm OD OR Ertapenem 1 gm OD + Azithromycin dihydrate 500mg OD IV OR Levofloxacin 500mg OD IV OR Moxifloxacin 400mg OD IV
High-risk CAP Any of the clinical feature of **Moderate-risk CAP plus** any of the following: *Severe Sepsis and Septic Shock OR* *Need for Mechanical Ventilation*	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* *Enteric Gram-negative bacilli* *Legionella pneumophilia* *Anaerobes (among those with risk of aspiration)* *Staphylococcus aureus* *Pseudomonas aeruginosa*	***Risk for P. Aeruginosa*** IV antipneumococcal antipseudomonal ß-lactam (BLIC,cephalosporin or carbapenem) + IV extended macrolides + aminoglycoside Piperacillin-Tazobactam 4.5 gm q6h OR Cefepime 2 gm q8-12h OR Meropenem 1 gm q8h + Azithromycin dihydrate 500mg OD IV + Gentamicin 3mg/kg OD OR Amikacin 15mg/kg OD OR
		IV antipneumococcal antipseudomonal ß-lactam (BLIC,cephalosporin or carbapenem) + IV Ciprofloxacin/ high dose Levofloxacin Piperacillin-Tazobactam 4.5 gm q6h OR Cefepime 2 gm q8-12h OR Meropenem 1 gm q8h + Levofloxacin 750mg OD IV OR Ciprofloxacin 400mg q8-12h IV

Risk Stratification	Potential Pathogens	Empiric Therapy
High-risk CAP Any of the clinical feature of **Moderate-risk CAP plus** any of the following: *Severe Sepsis and Septic Shock OR* *Need for Mechanical Ventilation*	*Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydophilia pneumoniae* *Mycoplasma pneumoniae* *Moraxella catarrhalis* *Enteric Gram-negative bacilli* *Legionella pneumophilia* *Anaerobes (among those with risk of aspiration)* *Staphylococcus aureus* *Pseudomonas aeruginosa*	If **MRSA pneumonia** is suspected, add Vancomycin 15mg/kg q8-12h OR Linezolid 600mg q12h IV OR Clindamycin 600mg q8h IV

SOURCE: *Joint Statement of the Philippine Society for Microbiology and Infectious Diseases, Philippine College of Chest Physicians, Philippine Academy of Family Physicians, Inc. and Philippine College of Radiology. Philippine Clinical Practice Guidelines. Diagnosis, Empiric Management and Prevention of Community-Acquired Pneumonia in Immunocompetent Adults 2016 Update Treatment.*

APPENDIX C-1: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary *(Source: www.ards.net.org)*

NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary

INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals ≤ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

APPENDIX C-2: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary *(Source: www.ards.net.org)*

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%

Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.

If Pplat > 30 cm H_2O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).

If Pplat < 25 cm H_2O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains ≤ 30 cm H_2O.

APPENDIX C-3: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary *(Source: www.ards.net.org)*

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pH GOAL: 7.30-7.45

Acidosis Management: (pH < 7.30)

If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (Maximum set RR = 35).

.

If pH < 7.15: Increase RR to 35.

If pH remains < 7.15, V_T may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).

May give $NaHCO_3$

Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

I: E RATIO GOAL: Recommend that duration of inspiration be ≤ duration of expiration.

PART II: WEANING

A. Conduct a SPONTANEOUS BREATHING TRIAL daily when:

1. $FiO_2 \leq 0.40$ and PEEP ≤ 8 OR $FiO_2 \leq 0.50$ and PEEP ≤ 5.
2. PEEP and FiO_2 ≤ values of previous day.
3. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
4. Systolic BP ≥ 90 mmHg without vasopressor support.
5. No neuromuscular blocking agents or blockade.

APPENDIX C-4: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary *(Source: www.ards.net.org)*

B. SPONTANEOUS BREATHING TRIAL (SBT):

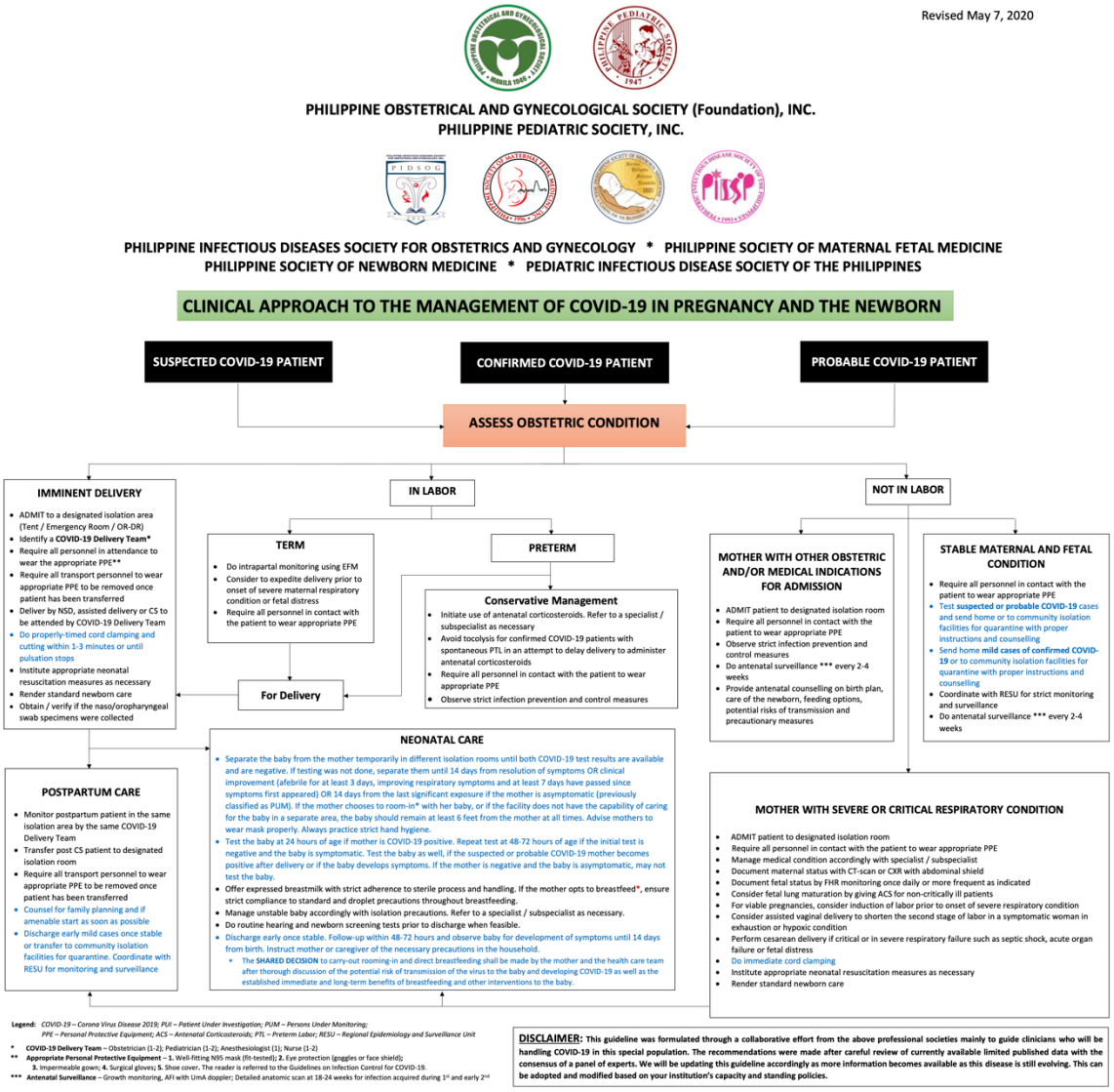
If all above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of UP TO 120 minutes of spontaneous breathing with FiO2 ≤ 0.5 and PEEP ≤ 5:

1. Place on T-piece, trach collar, or CPAP ≤ 5 cm H_2O with PS ≤ 5
2. Assess for tolerance as below for up to two hours.
    a. $SpO_2 \geq 90$: and/or $PaO_2 \geq 60$ mmHg
    b. Spontaneous $V_T \geq 4$ ml/kg PBW
    c. RR ≤ 35/min
    d. pH ≥ 7.3
    e. No respiratory distress (distress= 2 or more)
        - HR > 120% of baseline
        - Marked accessory muscle use
        - Abdominal paradox
        - Diaphoresis
        - Marked dyspnea
3. If tolerated for at least 30 minutes, consider extubation.
4. If not tolerated resume pre-weaning settings.

Definition of UNASSISTED BREATHING
(Different from the spontaneous breathing criteria as PS is not allowed)

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to 5 cm H_20 **without pressure support or IMV assistance.**

APPENDIX D: Algorithm on the Clinical Approach to the Management of COVID-19 in Pregnancy and the Newborn



APPENDIX E-1: Different Kinds of Face Mask

MASK TYPE	STANDARDS	FILTRATION EFFECTIVENESS		
Surgical Mask 	**China:** YY 0469	3.0 Microns: ≥95% 0.1 Microns: ≥30%		
	USA: ASTM F2100	Level 1	Level 2	Level 3
		3.0 Microns: ≥95% 0.1 Microns: ≥95%	3.0 Microns: ≥98% 0.1 Microns: ≥98%	3.0 Microns: ≥98% 0.1 Microns: ≥98%
	Europe: EN 14683	Type I	Type II	Type III
		3.0 Microns: ≥95% 0.1 Microns: ✗	3.0 Microns: ≥98% 0.1 Microns: ✗	3.0 Microns: ≥98% 0.1 Microns: ✗
Respirator Mask 	**USA:** NIOSH (42 CFR 84) **China:** GB2626	N95 / KN95	N99 / KN99	N100 / KN100
		0.3 Microns: ≥95%	0.3 Microns ≥99%	0.3 Microns ≥99.97%
	Europe: EN 149:2001	FFP1	FFP2	FFP3
		0.3 Microns: ≥80%	0.3 Microns: ≥94%	0.3 Microns: 99%

3.0 Microns: Bacteria Filtration Efficiency standard (BFE).

0.1 Microns: Particle Filtration Efficiency standard (PFE).

0.3 Microns: Used to represent the most-penetrating particle size (MPPS), which is the most difficult size particle to capture.

✗: No requirements.

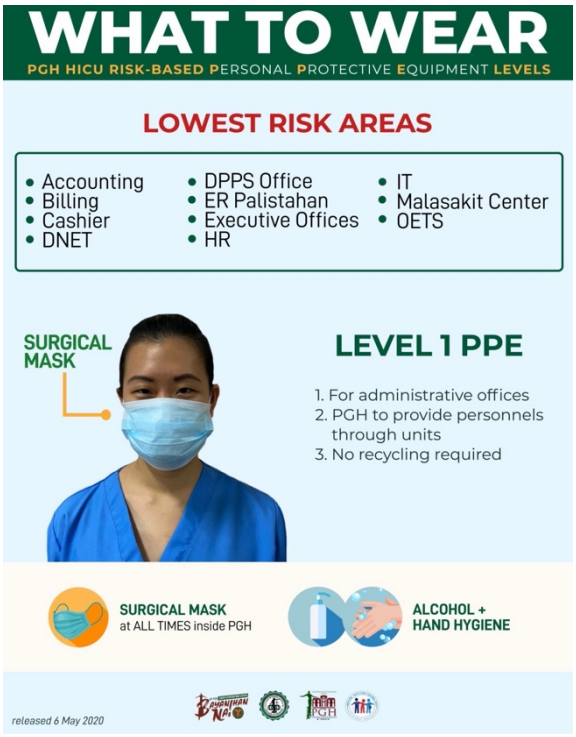
Image downloaded from: *https://smartairfilters.com/en/blog/comparison-mask-standards-rating-effectiveness/*

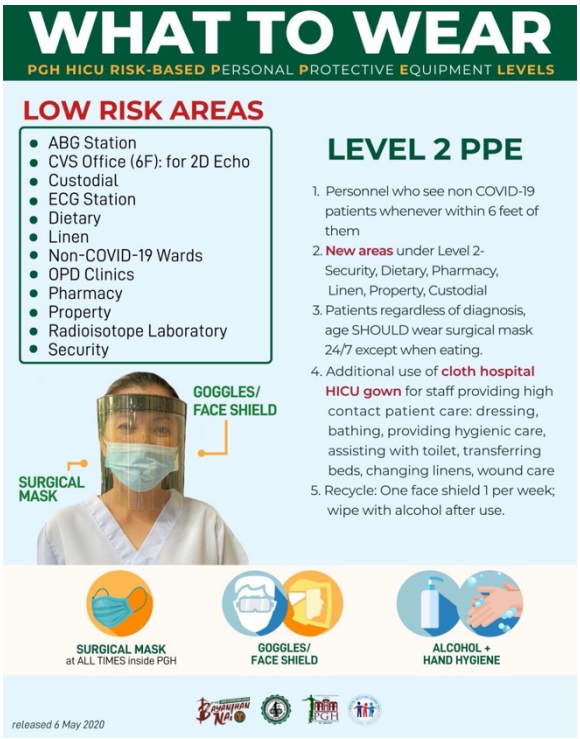
APPENDIX E-2: Different Kinds of N95 Face Mask

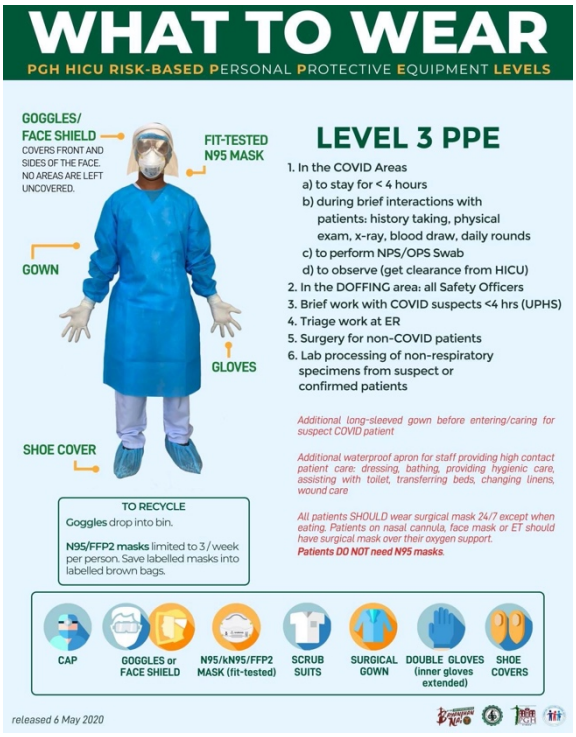
			
	Standard N95 Respirator 3M Model 8210	**Surgical N95 Respirator 3M Model 1860**	**Surgical N95 Respirator 3M Model 1870+**
Designed to help protect the wearer from exposure to airborne particles (e.g. Dust, mist, fumes, fibers, and bioaerosols, such viruses and bacteria)	✓	✓	✓
Designed to fit tightly to the face and create a seal between the user's face and the respirator	✓	✓	✓
Meets NIOSH 42 CFR 84 N95 requirements for a minimum 95% filtration efficiency against solid and liquid aerosols that do not contain oil	✓	✓	✓
Cleared by the U.S. FDA as a surgical mask	✗	✓	✓
Not made with natural rubber latex	✓	✓	✓
Fluid Resistant - Meets ASTM Test Method F1862 "Resistance of Medical Face Masks to Penetration by Synthetic Blood" which determines the mask's resistance to synthetic blood directed at it under varying high pressures.[1]	✗	120 mm Hg ✓	160 mm Hg ✓

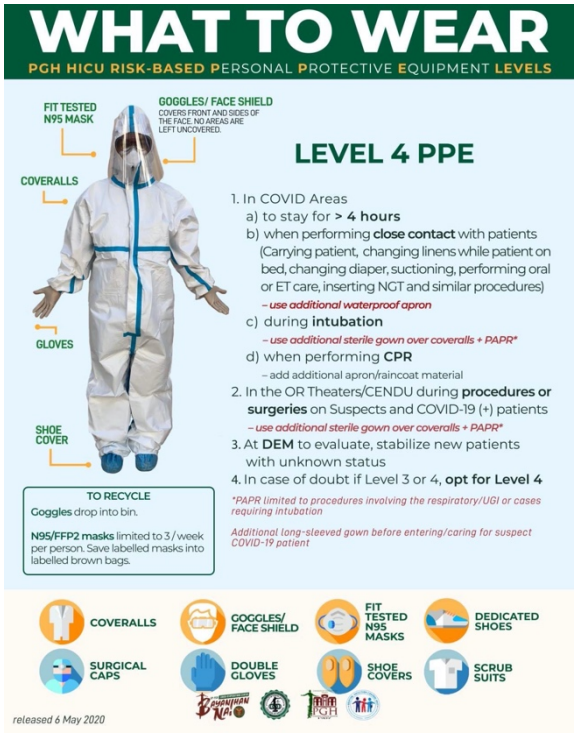
Source: *Surgical N95 vs. Standard N95 – Which to Consider? 3M Technical Bulletin, March 2020, Revision 2 https://multimedia.3m.com/mws/media/1794572O/surgical-n95-vs-standard-n95-which-to-consider.pdf*

APPENDIX F: PGH-HICU Risk-Based Personal Protective Equipment (PPE) Levels Infographic*







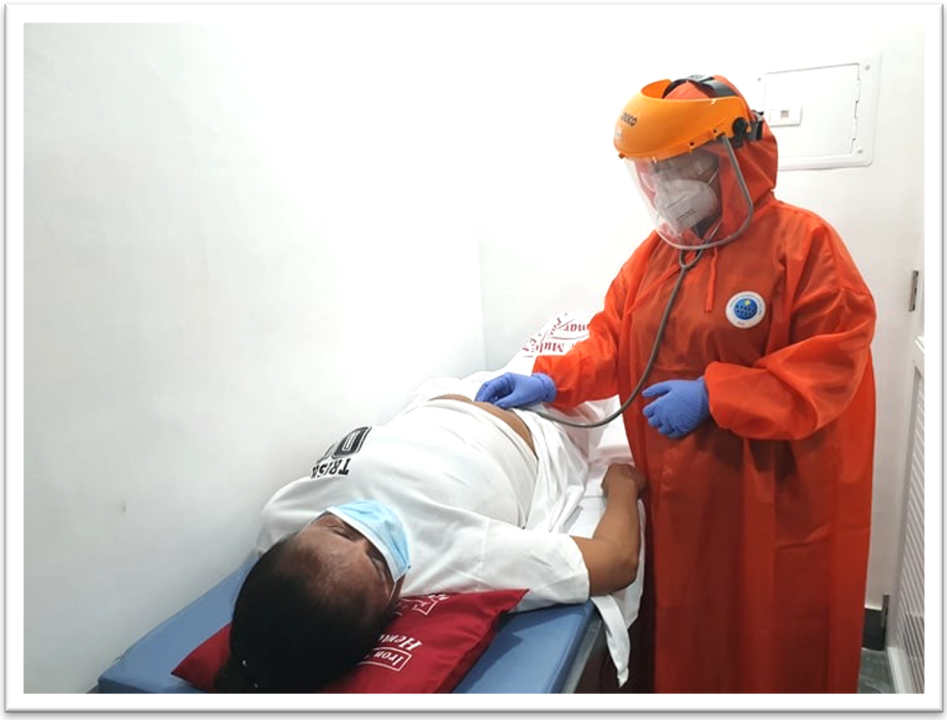


**Posted with permission from the Philippine General Hospital-Hospital Infection Control Unit*

APPENDIX G-1: Components of Level 3 PPE for OB-Gyn Procedures

Image showing the complete components of level 3 PPE

APPENDIX G-2: Level 3 PPE for OB-Gyn Procedures



An obstetrician wearing level 3 PPE while examining a pregnant patient

An obstetrician wearing level 3 PPE while performing ultrasound

APPENDIX H-1 Components of Level 4 PPE for OB-Gyn Procedures

Image taken shows the components of level 4 PPE prior to donning of sterile OR gown and gloves. The physician on the left is wearing a plastic apron over her overalls as an additional protective layer.

APPENDIX H-2 Components of Level 4 PPE for OB-Gyn Procedures

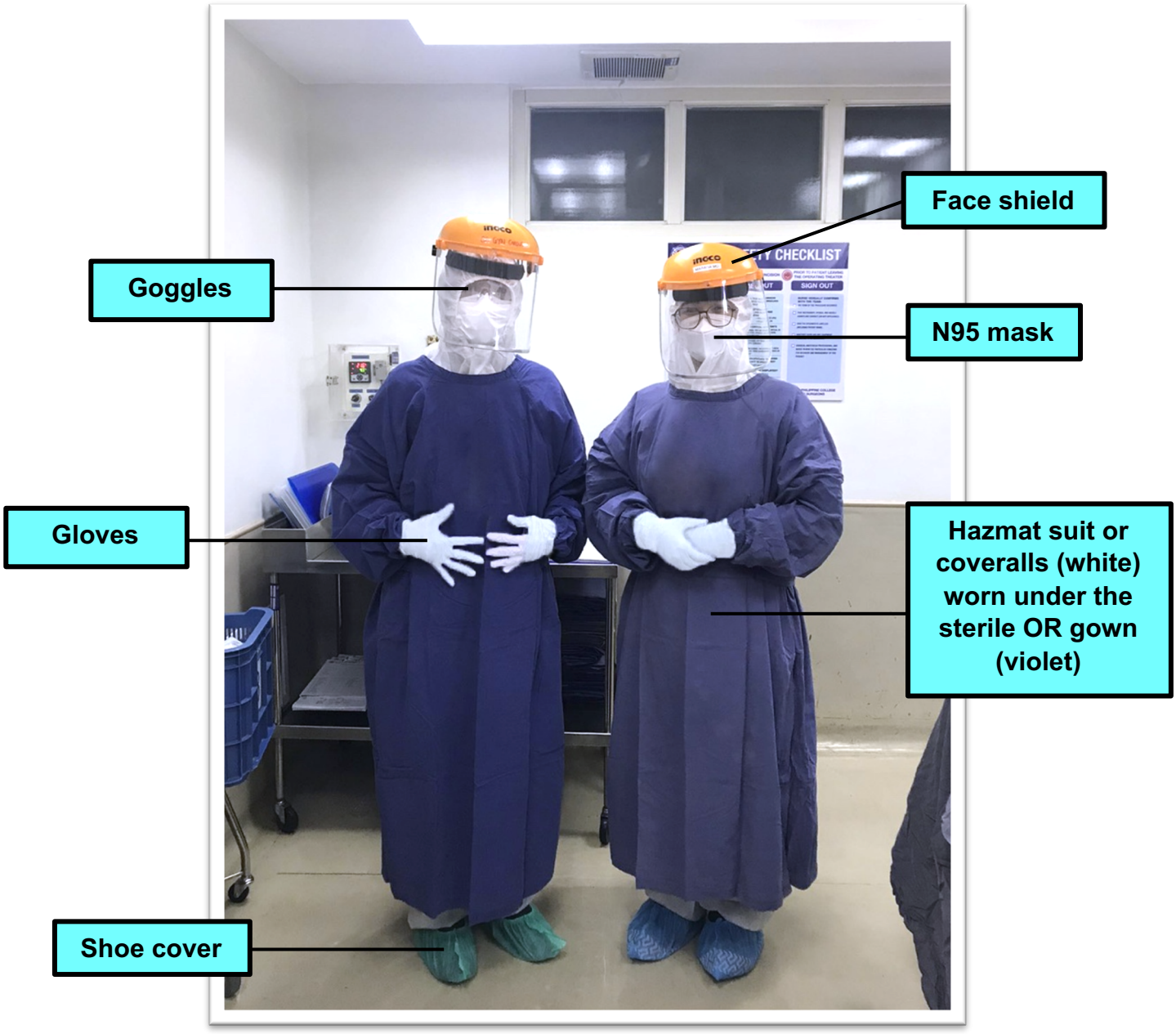


Image taken shows the components of level 4 PPE, with the addition of sterile OR gown worn over the coveralls and additional layer of sterile gloves.

APPENDIX H-3 Components of Level 4 PPE for OB-Gyn Procedures

Prior to donning sterile OR gown

After donning sterile OR gown

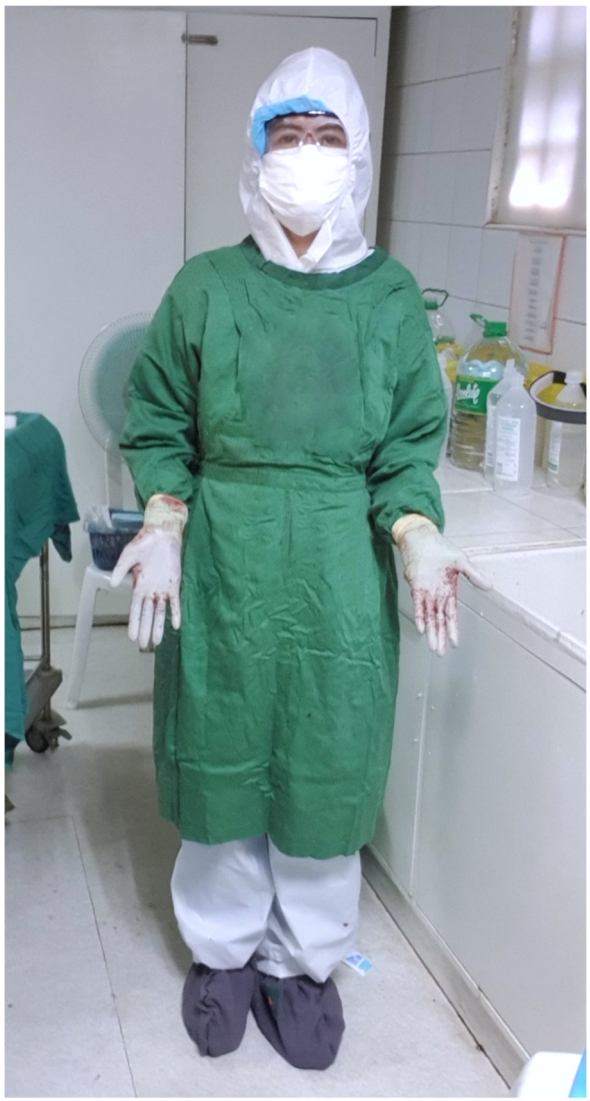


Image on the *left* illustrates the components of level 4 PPE prior to donning the sterile OR gown, namely: goggles, N95 mask, hair cap, coverall, scrub suit (worn underneath the coveralls), gloves, and shoe cover.

Image on the *right* illustrates the components of level 4 PPE, with the addition of sterile OR gown worn over the coveralls and another layer of sterile gloves.