Keeping up with COVID-19: A Review for Family Physicians

Nenacia Ranali Nirena R. Palma-Mendoza, MD, FPAFP[a]; Rojim J. Sorrosa, MD, FPAFP[b];
Martha Jane Pauline S. Umali, MD, FPAFP[c] and Kryszia Elouise Portal, MD[a]

Background: Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China in December 2019. This has rapidly spread worldwide, causing a pandemic. The Philippines ranks 3rd in Southeast Asia with more than 15,000 confirmed cases, and a case fatality rate of 6.01%, close to the global average of 6.33%.

Objective and Methods: This review aims to provide Family and Community Physicians the latest updates on epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment options, and prognosis of COVID-19. Online literature search was done with WHO and DOH websites prioritized for epidemiologic data, and MEDLINE for the most recent and relevant journal articles.

Pathogenesis: SARS-CoV-2, the etiologic agent of COVID-19, is an enveloped, positive sense single-stranded RNA virus which triggers immune-mediated responses responsible for most of the clinical manifestations of the disease. Angiotensin Converting Enzyme 2 appears to play a critical role in viral entry and disease severity.

Clinical Manifestations: There have been reports of asymptomatic cases. Majority have mild illness, with common symptoms of fever, cough, headache and fatigue. Those who progress to the critical stage of the disease present with Severe Acute Respiratory Syndrome, sepsis or Multiple Organ Dysfunction.

Diagnostic Evaluation: The definitive diagnosis of SARS-CoV-2 requires an analysis of respiratory specimens collected through oropharyngeal and nasopharyngeal swabs. The reverse transcriptase-polymerase chain reaction (RT-PCR) is considered the confirmatory test. Serological rapid detection test (RDT) for SARS-CoV-2 IgM and IgG may be done, but as an adjunct only because antibodies appear later in the course of disease. Imaging studies and other tests are used to monitor the severity of the condition, but not for diagnosis.

Treatment and Prognosis: Supportive therapy is the cornerstone of management. Currently, there is no FDA-approved drug or agent specifically for the treatment of COVID-19. Drugs being investigated for treatment are those that are currently used for other viral infections or indicated for other conditions. A vaccine is yet to be developed. Old age, the presence of comorbidities such as hypertension, diabetes, cardiovascular and lung diseases, and smoking history are risk factors that lead to severe complications and death.

Conclusion: COVID-19 has caused a global public health crisis. In the Philippines, cases are still on the rise. Majority of cases are mild. More severe and fatal disease is associated with old age and the presence of comorbidities. Definitive diagnosis is through RT-PCR. Supportive therapy is the cornerstone of management. The search continues for a proven, effective drug for treatment and vaccine for prevention of COVID-19.

Keywords: Coronavirus Disease 2019 (COVID-19), Severe Acute Respiratory Syndrome Coronavirus, SARS-CoV-2

_____
[a]Learning Enhancement Group, FamilyDOC Family and Community Medicine Residency Training Program
[b]Department of Family and Community Medicine, Southern Philippines Medical Center, Davao City
[c]Department of Family and Community Medicine, Philippine General Hospital, University of the Philippines Manila

INTRODUCTION

In December 2019, a novel coronavirus causing severe acute respiratory syndrome was identified in Wuhan, Hubei Province of China.[1] The virus belongs to the Coronaviridae family and is phylogenetically related to Severe Acute Respiratory Syndrome-like (SARS-like) bat viruses, so bats could be the possible primary source. This virus is now named SARS-CoV-2 and the disease it causes is Coronavirus Disease 2019 or COVID-19. The disease is similar to the previous human coronaviruses Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) in 2002 and Middle East Respiratory Syndrome Corona virus (MERS-CoV) in 2012. How it transferred to humans is not known, but the rapid human to human transfer has been confirmed widely.[2] This resulted into the present pandemic.

Epidemiology

On March 11, 2020, the WHO declared COVID-19 as a pandemic affecting several countries outside of China. To date, over 200 countries are affected by this pandemic. As of May 2020, there were more than 5.5 million people affected and more than 350 thousand reported deaths worldwide. The Americas and Europe have the highest number of cases.[3] Southeast Asia has around more than 220 thousand cases with the Philippines ranking third after Singapore and Indonesia. The Philippines recorded more than 15,000 confirmed cases nationwide with case-fatality of 6.01%,[4] very close to the global average of 6.33%.[3] More than half of the cases come from the National Capital Region, a region with the highest population density in the country. Based on a WHO Philippines report, the most affected age group is 30-39 years (21.6%) followed by 20-29 years (17.3%). Among the confirmed deaths, more than 60% are from the 60 years and above age group.[5]

To date, COVID-19 infection is an ongoing public health crisis of national and international significance. The varying understanding of the transmission and pathophysiological patterns is an area of concern. The lack of vaccine and proven treatment suggest that COVID-19 will be a significant health problem for some time. Projection models support the need for continued preventive and control measures at the individual and public health level to mitigate the effects of this disease.

METHODS

This review was conducted to provide updated information for Family and Community Physicians about COVID-19. A review of existing literature was made in order to answer questions about its epidemiology, pathogenesis, clinical characteristics, diagnosis, treatment and prognostic outcomes. The World Health Organization and Philippine Department of Health websites were utilized for epidemiologic data until May 28, 2020. MEDLINE was searched to retrieve the most recently published journals. Clinical trials and systematic reviews were prioritized. Practice guidelines from local societies were also reviewed. We focused on findings and recommendations that are relevant to family and community practice.

Pathogenesis

A thorough understanding of its pathogenesis is needed to guide the development of targeted, effective, and efficient interventions. SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus, belonging to the beta subfamily of coronaviruses. It can be inactivated by ultraviolet light and is sensitive to most disinfectants such as diethyl ether, 75% ethanol, chlorine, peracetic acid, and chloroform. It has been reported to be more stable on plastic and stainless steel than on copper and cardboard.[6] Upon entering the respiratory tract, the virus binds to a host cell through angiotensin converting enzyme 2 (ACE2) which acts as a functional receptor of the virus. Expression of ACE2 is high in the lungs, heart, ileum, kidneys and bladder.[7] Then the virus initiates a series of immune responses which determine the clinical picture, ranging from absence of symptoms, mild disease to severely fatal.

There are epidemiological trends in terms of the severity of disease manifestation. First, severe disease is associated with higher viral load.[8] Second, older people are more severely affected than infants and children. Some explanations for this include lower expression of ACE2 receptor in the pediatric population[7] and a dysregulated immune response among older people.[8] Immune dysregulation with subsequent lymphocytopenia and cytokine storm has been implicated in different studies as the underlying mechanism for acute respiratory distress syndrome and multi-organ dysfunction seen in severe cases.[7,9] Another notable trend is the worse outcomes of COVID-19 among those with underlying conditions such as hypertension, uncontrolled diabetes and cardiovascular diseases. This may be due to increased expression of antibody receptors in the monocytes and macrophages of these patients which promote antibody-dependent enhancement leading to higher infection of target cells.[6,8] The continuing search for an effective and safe treatment will depend on these postulated mechanisms of pathogenesis of the disease. Targets would be decreasing the viral load either by blocking viral entry and replication in host cells, as well as abating the immune response mounted by infected individuals.

Clinical Characteristics

Information about the clinical characteristics of COVID-19 is still evolving with some cases reporting unusual presentations of the disease. Infected children are usually asymptomatic, and there are more children than adults who have milder conditions, faster recovery, and a better prognosis.[10] The mean incubation period from infection to development of symptoms is 5.2 days,[11] with a range of 0-24 days.[12] However, a person becomes contagious as early as 2.5 days before the onset of symptoms. Mild cases have been reported to shed the virus 10 days after symptom resolution, while severe cases continue shedding up to 25 days after the initial symptoms.[12] While majority of the transmission of the virus is attributed to respiratory droplets from a symptomatic source, asymptomatic transmission has been reported in several studies. Thus, a careful history should also include possible exposure to the disease even among asymptomatic individuals.

The symptoms most frequently seen among COVID-19 patients are fever, cough, fatigue, sputum production, shortness of breath,

sore throat and headache. A small proportion of patients present with gastrointestinal symptoms like diarrhea and vomiting.[13] These symptoms present in varying levels of severity, as shown in Table 1.[14] Similar to the global trend, majority of cases in the Philippines (89%) have mild illness.[5]

Table 1. Levels of severity and clinical manifestation of COVID-19.

Level of Severity	Clinical Manifestation
Mild	fever, cough, nasal congestion, sore throat, headache, malaise, some gastrointestinal symptoms; NO evidence of viral pneumonia or hypoxia
Moderate	With clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but not severe, and $SpO_2 \geq 90\%$ on room air
Severe	Severe pneumonia with RR > 30 breaths/min., severe respiratory distress, or $SpO_2 < 90\%$ on room air
Critical	Acute Respiratory Distress Syndrome, Sepsis

Diagnosis

Swab Analysis via RT-PCR

The diagnosis of COVID-19 is confirmed by the analysis of respiratory samples through real-time reverse transcriptase-polymerase chain reaction (RT-PCR).[15,16] It is also the recommended confirmatory test in the Philippines.[17] There are various samples that can undergo analysis by RT-PCR i.e. bronchoalveolar lavage (93% positive rate), sputum (72%), nasal swabs (63%) and pharyngeal swabs (32%).[15] The most common sampling method in clinical practice is nasal and oropharyngeal swab collection. Between the two, the oropharyngeal swab specimen is of low priority and must be combined with a nasopharyngeal swab specimen in the same tube.[18] The virus can be first detected 1 to 2 days prior to the onset of upper respiratory tract infections and up to 7-12 days for moderate cases and 2 weeks in severe cases.[15] As of 27 May 2020, the Philippine Food and Drug Administration has approved 46 RT-PCR kits[19] and are being used in the 31 laboratories in the Philippines licensed to perform RT-PCR tests.[20] A zoning system for these laboratories is established for proper referral of samples from all regions of the Philippines.[21] Each kit is manufactured to detect either one particular gene or multiple genes and can either be used as a screening or a confirmatory assay. When only the screening assay is positive or when both the screening and confirmatory assays are negative, the result is considered negative. Table 2 summarizes the recommended interpretation of RT-PCR results.[22] Due to the cost and inaccessibility of equipment needed for RT-PCR, and the highly contagious nature of the disease, there is a need to develop tests that can be used for point-of-care testing which includes antibody-testing by serology, isothermal amplification, barcoding and microfluidic technologies.[18,23]

Serum Immunology

Serological diagnosis in the form of rapid detection test (RDT) kits were developed to detect the presence of SARS-CoV-2 IgG, IgM or both may be used as a supplement in the detection of the virus in patients with high clinical suspicion but negative for RT-PCR. In the Philippines, it is recommended to be used as adjuncts for testing symptomatic and asymptomatic patients with relevant history and travel exposure.[21] In an analysis of nine different kits, the sensitivity for IgM and IgG tests ranges between 72.7% and 100% and specificity ranges 98.7% to 100%. An immunology test is considered positive when IgM is positive with an increased IgG titer more than 4 times than that in the acute phase. While RDT kits are relatively cheaper, safer and easier to perform compared to RT-PCR, these tests have limited utility since antibodies appear later in the disease.[15]

Table 2. Recommended interpretation of RT-PCR results.

Screening Test Results	Confirmatory Test Results	Interpretation
Positive	Positive	Positive for COVID 19
Positive	Negative	Negative for COVID 19
Negative	Negative	Negative for COVID 19
Negative	Positive	Retest or refer for additional testing

Other Tests

On imaging studies, a characteristic bilateral ground-glass opacity is seen in chest x-rays of COVID-19 patients. This is more clearly seen in CT scans, where segmental consolidation is also observed.[25] Other laboratory findings among COVID-19 patients include neutrophilia, lymphocytopenia, elevated prothrombin time, LDH, D-dimer, ALT and creatine kinase. Levels of inflammatory cytokines and C-reactive protein are directly correlated with disease severity and progression.[26] However, these diagnostic tests are non-specific and must not be used to confirm the diagnosis of COVID-19.

Treatment

In general, supportive management is the mainstay for the treatment of COVID-19. For persons with suspected or confirmed disease, self-isolation is recommended.[27] If these patients develop symptoms that are mild, they can continue home isolation and be monitored by their family physicians via teleconsultation. Isolation in available community quarantine facilities may also be done if not feasible at home. Local guidelines recommend close monitoring and hospital admission if with risk factors like age above 65 years, coexisting comorbid diseases, or presence of moderate to severe symptoms as the clinical course may rapidly progress.[28] Those with severe symptoms require oxygen and ventilatory support, and those who are critically ill need immediate intensive care unit (ICU) admission.[29]

Currently, there is no FDA-approved drug or agent specifically for the treatment of COVID-19. Drugs being investigated for treatment are those that are currently used for other viral infections or indicated for other conditions and are considered off-label use. These drugs are used mainly in the hospital setting and as part of clinical trials. Various studies are also in progress on vaccine development, prophylaxis, alternative and complementary medicine, among others. Treatment guidelines in the Philippines made rapid appraisals on the use of

chloroquine, hydroxychloroquine, the antiviral lopinavir/ritonavir and immunomodulator tocilizumab, and recently added favipiravir, remdesivir and convalescent plasma transfusion.[30] It is important to raise caution to family and community physicians in the use of pharmacologic options for COVID-19 as they are still under investigation. As part of antimicrobial stewardship program, we encourage all physicians to continue to assess clinical data as it emerges.[31]

Chloroquine/Hydroxychloroquine

Chloroquine and hydroxychloroquine, employed initially for the treatment of malaria, gained worldwide attention for the treatment of COVID-19 only on a mechanistic basis. It is hypothesized to block the entry of the virus into the cell, decrease viral replication and budding and has anti-inflammatory action.[32] In one of the first published evidence on the drug, patients who received chloroquine phosphate

had lower rates of pneumonia exacerbation, greater improvement in lung imaging findings, higher rates of conversion to the virus-negative state, and shorter disease course compared to those who did not receive the drug.[33] In another single-arm, open-label clinical on 42 patients, the majority of patients were asymptomatic or had mild upper respiratory tract symptoms. Only a minority (22.2%) had bronchitis and pneumonia.[34] There is however a concern for harm, particularly QTc prolongation and cardiac arrhythmias especially when given at high doses.[35]

Azithromycin

Azithromycin is an antibiotic against infections caused by susceptible bacteria, such as respiratory infections. The basis for considering the drug was because of its in vitro activity against Zika and Ebola viruses.[36] Previous studies have also shown that it prevents

Table 3. Recommended interpretation of rapid detection test kits.

Clinical Condition	Results		Interpretation
	IgM	IgG	
Symptomatic Patients with Relevant History of Travel/ Exposure	(-)	(-)	Swab for RT-PCR • If RT-PCR (+), manage as a **Confirmed COVID-19 Case** • If RT-PCR (-), not a COVID-19 case but must complete 14-day isolation. There is no need to repeat the antibody test. • If RT-PCR unavailable, isolate the patient for 14 days or until asymptomatic, whichever is longer.
	(-)	(+)	
	(+)	(-)	Classify the patient as a **Probable COVID-19 Case**. Swab for RT-PCR • If RT-PCR (+), manage as a COVID-19 Case. • If RT-PCR (-), not a COVID-19 Case but must complete 14-day isolation. Repeat antibody test after. • If RT-PCR unavailable, isolate patient for 14 days or until asymptomatic, whichever is longer.
	(+)	(+)	
Asymptomatic Patients with Relevant History of Travel/ Exposure	(-)	(-)	Repeat testing on Day 14 of the quarantine period. If still negative, release from quarantine.
	(+)	(+)	Classify the patient as a **Presumed Recovered Case**. The patient can be released from quarantine and there is no need to repeat the test at the end of the quarantine period.
	(-)	(+)	
	(+)	(-)	**Probable COVID-19 Case**, repeat the antibody tests on Day 14 of quarantine period • If still IgM (+) and IgG (-), extend quarantine by 7-day increments. • If IgG (+), the patient may be released from quarantine regardless of IgM result.

*DOH Revised Interim Guidelines on Expanded Testing for COVID-19

Table 4. Disease Classification Based on Status of Infection.

Classification	Description
Suspect Case	The patient manifests with respiratory symptoms and with pertinent history of travel 14 days prior to symptom onset or a contact with a confirmed or probable case two days prior to onset of illness. Individuals with fever or respiratory symptoms that are aged 60 and above, with comorbidities, with high risk pregnancy or health workers are also classified as suspect cases.
Probable Case	The patient being a suspect was either inconclusive or was not done in an accredited laboratory for COVID-19 confirmatory testing.
Confirmed Case	The patient tests positive for COVID-19 in a test done by an accredited testing facility, regardless of the presence or absence of symptoms.
Presumed Recovered Case	The patient is asymptomatic, with a relevant history of exposure or travel and tests positive for IgG using antibody-based kits.

severe respiratory tract infections in patients suffering from viral infection.[37] In the previously cited controlled but non-randomized study of Gautret, 26 patients received hydroxychloroquine (200 mg three times daily for 10 days) of which six received it in conjunction with azithromycin (500 mg on day 1 followed by 250 mg daily for 4 days). Patients treated with hydroxychloroquine alone or in combination with azithromycin had significantly greater viral clearance at day 6 (57.1 and 100%, respectively), compared to those in the control group (12.5%).[34] Azithromycin, however, may have an additive effect on cardiac toxicity when combined with hydroxychloroquine.

Antivirals

Locally, the antivirals included for COVID-19 management are remdesivir, lopinavir-ritonavir and favipiravir.[30] Remdesivir is a broad-spectrum antiviral originally developed for treatment against the Ebola virus in 2017 but is also considered promising in treating SARS and MERS-CoV5. It is an adenosine analogue which acts on nascent viral RNA resulting in premature termination. While its direct effect on clearing viral load is still not established, its use in the USA suggests that it contributes to decreasing the oxygen and mechanical ventilation requirements for COVID-19 patients.[38] It is recommended to be given as an infusion with a loading dose of 200 mg IV on Day 1 followed by a maintenance dose of 100 mg IV once daily for 10 days. However, it may be extended for an additional 4 days at 100 mg IV once daily if COVID-19 remains detectable at day 10 of treatment.[30] Lopinavir-Ritonavir is marketed as a combination pill and is originally developed for the treatment against HIV. Lopinavir is a protease inhibitor with poor oral bioavailability and is administered in combination with ritonavir which acts by inhibiting the enzymes that promote lopinavir metabolism. Although it was shown to decrease the risk of acute respiratory distress in SARS-CoV cases, Lopinavir-Ritonavir offers no clinical benefit over standard care in treating COVID 19 patients.[38] It is given

as a 200mg/50mg tablet, 2 tablets twice a day for 14 days. Favipiravir is a guanine analog developed in Japan for the treatment of influenza resistant to treatment with neuraminidase inhibitors and works by interrupting viral RNA replication at the level of the RNA-dependent RNA polymerase (RdRp). In Japan and China, Favipiravir was shown to decrease the duration of fever and cough among COVID 19 cases. Oseltamivir, a neuraminidase inhibitor, is approved for the treatment of influenza A and B. Its effect on SARS-CoV-2 is still under investigation but it is usually in combination with either chloroquine or favipiravir.[38] It is currently recommended only as part of supportive therapy for COVID-19 patients with Pneumonia and coexisting Influenza infection to be given at 75mg/tab PO twice a day for 5-10 days.[39] Internationally, Umifenovir is also under investigation for COVD-19 treatment. It was developed in Russia in 1988 as treatment for Influenza and is currently being investigated as both a stand alone drug and as a combination with lopinavir-ritonavir.[38] In a review of safety profiles, it was found to be comparable among the antivirals favipiravir, oseltamivir, umifenovir, lopinavir/ritonavir and placebo in terms of overall (28.2%) and serious (0.4%) adverse effects, and discontinuations due to AEs (1.1%) observed up to 21 days.[41]

Vaccines

The speed with which vaccine development for COVID-19 is progressing is unprecedented. As of May 15, 2020, the World Health Organization reported that worldwide, there are 8 candidate vaccines in clinical evaluation, and 110 in preclinical evaluation. The vaccines in the clinical evaluation stage are using one of the following platforms: non-replicating viral vector, RNA, DNA and inactivated.[42] Additional platforms being explored are live attenuated virus, replicating viral vector, recombinant protein, peptide-based, and virus-like particle.[43] Passive immunization by direct administration of monoclonal antibodies against SARS-CoV-2 is also being studied.[44]

Table 5. Investigational drugs for the treatment of COVID-19.

Drugs	Dosing Regimen	Expected Effects	Side Effects
Chloroquine (Inhibits viral entry to cell, anti-inflammatory)	Day 1: 1g PO Day 2–5 (or 7): 500mg PO qd	Clearance of viral load, CT scan improvement, early hospital discharge, improved survival	Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia, gastrointestinal effects, hypoglycemia, hemolysis (G6PD deficient), myopathy, rash
Hydroxychloroquine (Inhibits viral entry to cell, anti-inflammatory)	Day 1: 800mg PO Day 2–5 (or 7): 400mg qd PO	Symptom improvement, CT scan improvement, early hospital discharge, improved survival	Same with CQ (except without hemolysis) Anxiety, agitation, hallucinations, psychosis Allergic reaction
Azithromycin as adjunct to hydroxychloroquine (Inhibits viral entry to cell)	Day 1: 500mg PO Day 2–5: 250mg PO qd	Clearance of viral load, improved survival	Gastrointestinal effects, hepatotoxicity Prolonged QTc interval
Lopinavir/Ritonavir (Inhibits viral protein synthesis)	Day 1–10 (or 14): 400mg/100mg PO bid	Clearance of viral load, decrease ICU admission, improved survival	Nausea, vomiting, diarrhea, transaminase elevation, QTc interval prolongation and Torsades de Pointes, PR interval prolongation
Remdesivir (Inhibits RNA synthesis)	Day 1: 200mg IV Day 2–5 (or 10): 100mg IV qd	Clearance of viral load, early hospital discharge, improved survival	Transient transaminase elevation Mild, reversible PT prolongation Gastrointestinal symptoms

There are a number of challenges being faced by vaccine developers. First is determining the optimal antigen design. Second is the risk of exacerbating lung disease either by direct injury or indirectly through antibody-dependent enhancement. Third is the uncertainty on the duration of immunity that can be conferred by a vaccine.[45] Aside from effectiveness, one major consideration in vaccine development is safety. Thus, while we are all hoping for a new vaccine to be produced sooner rather than later, a very rigorous process must still be observed and enforced for the benefit of all its intended recipients.

Prognosis

A meta-analysis of 13 studies with 3,027 patients has been done to evaluate the prognostic factors of COVID-19. The results showed that patients who are males, aged over 65, and smokers might face a greater risk of developing into the more critical condition. Comorbidities such as hypertension, diabetes, cardiovascular disease, and respiratory diseases also increase the probability of the disease progressing to a more critical condition. Worsening of clinical manifestation such as fever, shortness of breath or dyspnea, and derangement in laboratory examinations have also been associated with more serious disease.[46] Family physicians should take note of these factors to provide the appropriate treatment and advice to their patients and families.

Conclusion

COVID-19 pandemic is an ongoing public health crisis which has affected many countries around the globe. In the Philippines, the number of cases continues to rise. Majority of patients present with either mild or asymptomatic disease. A more severe or fatal disease course is observed among older patients and those with existing comorbidities. Prompt diagnosis using RT-PCR from respiratory specimens is needed to confirm the presence of the virus. Although there are ongoing clinical trials, treatment remains a challenge because there are no approved drugs to cure patients with COVID-19 infection, nor vaccines to prevent it. Supportive therapy is the mainstay of treatment.

References

1. Xu Y. Unveiling the origin and transmission of 2019-nCoV. Trends Microbiol 2020; 28(4): 239-40.
2. Shereen MA, Khan S, Kazmi A, et al. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 16; 24: 91.
3. WHO (May 28, 2020) WHO Corona Disease (COVID-19) Dashboard. https://covid19.who.int/
4. DOH (May 27, 2020). https://www.doh.gov.ph/covid19tracker.
5. World Health Organization Philippines. (May 2020). https://www.who.int/docs/default-source/wpro---documents/countries/philippines/emergencies/covid-19/who-phl-sitrep-33-covid-19-20may2020.pdf?sfvrsn=20e9ddd0_2
6. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020 ; 12(4). pii: E372.
7. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020; 215: 108427.
8. Kadkhoda K. COVID-19: an Immunopathological view. mSphere. 2020 Apr 22;5(2). pii: e00344-20.
9. Tufan A, Avanoğlu Güler A and Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic Drugs. Turk J Med Sci 2020; 50(SI-1): 620-32.
10. Zhen-Dong Y, Gao-Jun Z , Run-Ming J, et al. Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: A review. J Infect 2020 Apr 28. pii: S0163-4453(20)30241-3.
11. Li Q, Med M, Guan X, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. New Engl J Med 2020; 382 (13): 1199-207.
12. Siordia JA Jr. Epidemiology and clinical features of COVID-19: A review of current literature. J Clin Virol 2020; 127: 104357.
13. Tu H, Tu S, Gao S, et al. The epidemiological and clinical features of COVID-19 and lessons from this global infectious public health event. J Infect 2020 Apr 18. pii: S0163-4453(20)30222-X.
14. World Health Organization. Clinical Management of COVID-19. Interim Guidance 27 May 2020, pp. 13-4.
15. Zainol Rashid Z, Othman SN, Abdul Samat MN, Ali UK and Wong KK. Diagnostic performance of COVID-19 serology assays. Malays J Pathol 2020; 42(1): 13-21.
16. Chakraborty C, Sharma AR, Sharma G, Bhattacharya M and Lee SS. SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options. Eur Rev Med Pharmacol Sci 2020; 24(7): 4016-6.
17. Department of Health (April 2020). http://www.doh.gov.ph/2019-nCov/interim-guidelines
18. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections - the state of the art. Emerg Microbes Infect 2020; 9(1): 747-56.
19. Food and Drug Administration (May 2020). https://www.fda.gov.ph/?s=approved+PCR+test+kit+for+covid+19
20. World Health Organization. (May 2020). https://www.who.int/docs/default-source/wpro---documents/countries/philippines/emergencies/covid-19/who-phl-sitrep-33-covid-19-20may2020.pdf?sfvrsn=20e9ddd0_2
21. Department of Health (April 2020). https://www.doh.gov.ph/node/20826
22. Hong KH, Lee SW, Kim TS, et al. Guidelines for laboratory diagnosis of coronavirus disease 2019 (COVID-19) in Korea. Ann Lab Med 2020; 40(5): 351-60.
23. Udugama B, Kadhiresan P, Kozlowski HN, et al. Diagnosing COVID-19: The disease and tools for detection. ACS Nano 2020; 14(4): 3822-35.
24. Wang H, Li X, Li T, Zhang S, Wang L, Wu X and Liu J. The genetic sequence, origin and diagnosis of SARS-CoV-2. Eur J Clin Microbiol Infect Dis 2020 Apr 24 : 1–7.
25. Chen H, Ai L, Lu H, et al. Clinical and imaging features of COVID-19. Radiol Infect Dis 2020 Apr 27.
26. Hassan SA, Sheikh FN, Jamal S, et al. Coronavirus (COVID-19): A review of clinical features, diagnosis, and treatment. Cureus 2020; 12(3):e7355.
27. Centers for Disease Control and Prevention (April 8, 2020). Discontinuation of isolation for persons with COVID-19 not in healthcare settings (interim guidance). https://www.cdc.gov/coronavirus/2019-ncov/hcp/ disposition-in-home-patients.html.
28. Philippine Society of Microbiology and Infectious Disease (May 15, 2020). Unified COVID-19 Algorithms. Guidelines for Primary Care. https://www.psmid.org/unified-covid-19-algorithms-1.
29. Philippine Society of Microbiology and Infectious Disease (May 15, 2020). Unified COVID-19 Algorithms. Guidelines for Hospital Care. https://www.psmid.org/unified-covid-19-algorithms-2
30. Philippine Society for Microbiology and Infectious Diseases Interim Gudielines on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection. https://www.psmid.org/cpg-for-covid-19-ver-2-1-as-of-march-31-2020.
31. McCreary EK and Pogue JM. Coronavirus disease 2019 treatment: A review of early and emerging options. Open Forum Infect Dis 2020 Mar 3;7(4):ofaa105.
32. Shukla AM, Archibald LK, Shukla AW, Chloroquine and hydroxychloroquine in the context of COVID-19. Drugs Context 2020 Apr 28;9. pii: 2020-4-5.
33. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020; 14(1): 72–3.
34. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020: 105949.
35. Pastick KA, Okafor EC, Wang F, et al. Review: Hydroxychloroquine and chloroquine for treatment of SARS-CoV-2 (COVID-19). Open Forum Infect Dis 2020 Apr 15;7(4):ofaa130.
36. Retallack H, Di Lullo E, Arias C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci U S A. 2016; 113(50): 14408–13.

37.   Bacharier LB, Guilbert TW, Mauger DT, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA 2015; 314(19): 2034–44.

38.   Wu R, Wang L, Kuo HS, et al. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep 2020 May 11:1-15.

39.   Philippine Society for Microbiology and Infectious Diseases. (March 2020). https://www.psmid.org/cpg-for-covid-19-ver-2-1-as-of-march-31-2020/

40.   Department of Health. (May 2020). https://www.doh.gov.ph/node/21738

41.   Pelkington V, Pepperrell T, Hill A. A review of the safety of Favipiravir - A potential treatment in the COVID-19 pandemic? J Virus Erad 2020 Apr; 6(2): 45–51..

42.   World Health Organization (May 2020).   https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines.

43.   Le T, Andreadakis Z, Kumar A, et al. The COVID-19 vaccine development landscape. Nature Reviews, Drug Discovery. May 2020; 19: 305-6.

44.   Dhama K, Sharun K, Tiwari R, et al. COVID 19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Human Vaccines and Immunotherapeutics 2020:

45.   Lurie N, Saville M, Hatchett R and Halton J. Developing COVID-19 vaccines at pandemic speed. New Engl J Med March 2020.

46.   Zheng Z, Peng F, Xu B, et al. Risk factors of critical and mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020 Apr 23. pii: S0163-4453(20)30234-6.