Review Article

An updated overview on 2019 novel coronavirus

Sanjukta Mishra

Professor, Dept. of Biochemistry, Kalinga Institute of Medical Science
KIIT University, Bhubaneswar, Odisha, India

(Received: July 2020 Revised: September 2020 Accepted: October 2020)

Corresponding author: **Sanjukta Mishra**. Email: drmsanjukta@gmail.com

ABSTRACT

Coronavirus (CoV) has been associated with several infectious disease outbreak in humans in the past two decades, including Severe respiratory syndrome coronavirus [SARS-CoV] in 2002-2003 and Middle East respiratory coronavirus [MERS-CoV] in 2012. An unexpected and unexplained respiratory infection commenced at Wuhan city, China, during the end of 2019, which was named as novel coronavirus disease [2019-nCoV or COVID-19] by the World Health Organization (WHO). It is considered to be a zoonotic disease, as it has nearly similar amino acid homology to SARS-CoV. Reports have revealed an unexpected increase in number of cases worldwide (214 countries and territories along with 2 international conveyances), which intimidates the public with human to human escalation through respiratory droplets and contact routes. This pandemic was declared as a public health emergency of international concern. It follows an extremely heterogeneous course from mild Flu like symptoms [fever, cough, sore throat, dyspnoea, fatigue, headache and malaise] to severe acute respiratory distress syndrome. According to epidemiological data, old age and pre-existing medical co-morbidities are considered to be the risk factors for COVID-19. Currently, laboratory-based "Real time-reversed transcription Polymerase chain reaction" [rtRT-PCR] remains the molecular test of choice for the etiologic diagnosis. That apart, several hematological, biochemical markers along with various inflammatory cytokines (lymphopenia, serum level of C-reactive protein, D-dimer, ferritin, Interleukin-6, cardiac troponin I) may be used to assess disease severity. As of now, there have been approximately more than 36 million cases worldwide and more than one million succumbed to the illness (2.91% estimated mortality rate). Based on reports, India has become the second worst coronavirus hit country with a total number of cases reaching 68 lakhs. The dearth of selected medication (anti-CoV) and unusual transmission ability of 2019-nCoV continue to be responsible for this uninterrupted escalation. Woefully, specific vaccines are yet to come up. Treatment options like broad-spectrum antiviral Remdesivir, and oxygen therapy are being evaluated to control this unprecedented health crisis, although none of these drugs are FDA (Food and drug administration) approved. The path of this pandemic is very undetermined and unpredictable. In the present scenario, efficacious prevention needs swift action from the standpoint of public health strategies, which entails strict surveillance, rapid detection, and implementation of a containment plan to curb this outbreak. This review article highlights the updates on novel coronavirus 2019 and the uninterrupted apocalyptic progress concerning the present situation. It also highlights various perspectives of effective therapeutic strategies to restrain this viral outbreak.

Keywords: Coronavirus; COVID-19; pandemic; polymerase chain reaction

INTRODUCTION

An unexpected outbreak of pneumonia emerged in the people of Wuhan, China's Hubei province, during the end of 2019, which was contemplated to be initiated via zoonotic transmission connected to the seafood market (1). The etiology was attributed to be a novel coronavirus (2019-nCoV) by metagenomic sequencing of bronchoalveolar lavage fluid of patients. This was then named as severe acute respiratory syndrome coronavirus (SARS-CoV-2) by the International Committee on Taxonomy of Virus [ICTV], due to its high homology to SARS-CoV, responsible for acute respiratory distress syndrome (ARDS) in 2002-2003 (2). Eventually, World Health Organization (WHO) cited the disease as COVID-19, the abbreviation of 2019-nCoV and declared it as pandemic as the virus was highly transmissible, affecting a large number of

people globally by the rapid human to human spreading (3).

As of now, around 36 million COVID-19 cases have been reported worldwide (4). Covid-19 has been categorized as a global health crisis. Exorbitant probability of death in vulnerable groups [extreme ages, comorbid conditions like diabetes, hypertension, chronic kidney disease, coronary artery disease, and immunocompromised state] has been a serious concern. Prevention has been the current strategy of treatment in the absence of a definite proven anti-CoV therapeutic approach. Many countries have enforced lockdown and social distancing to alleviate virus spreading. This article updates the readers on current shreds of evidence on COVID-19, specifically pathogenesis, biochemical markers, and clinical aspects. As more data continue to emerge, it is recommended to refurbish the fact

regarding this vicious virus, which may usher the public for alertness.

Virus Transmission, pathogenesis and host cell immune response

Coronavirus is enveloped, positive, single-stranded RNA virus [60nm to 140nm in diameter], which appears like a crown under an electron microscope with spike glycoprotein on the envelope. It belongs to the subfamily Coronaviridae family in Nidovirales order, which is classified into 4 genera depending on genomic structure: alpha, beta, gamma, and delta, out of which alpha and beta coronavirus infects humans (5). 229E and NL63 belong to alpha CoV may be responsible for the common cold, whereas SARS-CoV and MERS-CoV belong to beta CoV (3). The novel coronavirus [2019-nCoV], responsible for the recent pandemic, is confirmed to be a member of beta coronavirus. It is named as SARS-CoV-2 due to its high homology (less than 80% nucleotide sequence) to SARS-CoV, a beta coronavirus which causes acute respiratory distress syndrome, with high mortality during 2002-2003 (6). Furthermore, amino acid sequence study reveals high sequence identical domains between 2019 nCoV and SARS-CoV, particularly the receptor binding domain of spike protein (6). Virus genome characterization and phylogenetic analysis of full-length genome sequencing on RNA sample showed that bat coronavirus (BatCoV RaTG13), which was previously detected in *Rhinolophus affinis* from Yunnan province, and 2019 nCoV were having high sequence identity (7). This close metagenomic RNA sequencing and phylogenetic relationship to RaTG13 provides evidence that bats might be a feasible host for the 2019-nCoV reservoir (8). So, it could be assumed that the consumption of wild animals might be a means to get going the spread of the virus from bats to human beings. Notably, there is a likelihood of another unidentified intermediate host, as the outbreak was related to the Hunan seafood wholesale market, where live animal species (hedgehogs, badgers, snakes, marmot, rabbit, turtledoves) were available (9). Further extensive studies are required to ascertain the natural reservoir and intermediate host. Though initial few cases were inked to animal-human transmission, further investigation unfolded human to human transmission, as successive cases reported with no history of being exposed to wild animals.

The current onset and expeditious increase of COVID-19 has established a global health predicament. Close contact with an infected person, exposed to coughing, sneezing, respiratory droplet, and aerosol are presumed to be the key factor responsible for human to human spread (10). Recent reports express concern about the spread of the virus from pre-symptomatic (1-3 days before the onset of symptoms) persons, which is the area of uncertainty

in understanding (11). It has also been reported that there is a possibility of infection from asymptomatic patients through feco-oral transmission [SARS-CoV RNA in stool even after negative respiratory sample] (12). Possibility of virus transmission is there if one comes in contact with COVID-19 patients and contaminated insentient objects like floor, plastic, stainless steel, cardboard etc.

The viral genomic structure must be reviewed elaborately to understand pathogenesis. Structural protein comprises of spike membrane, envelop protein, matrix protein, nucleocapsid protein, and eight necessary proteins (2). These structural proteins constitute a mature virion. Spike glycoprotein on the outer surface of the virus, with S1 and S2 subunits, takes the accountability of attachment and invasion into the host cell, which is the major mechanism of transmission (13). S2 subunit is highly conserved as it mediates virus-cell membrane fusion, followed by release of viral genome RNA into cytoplasm. The role of envelope is also essential for viral assembly. Fluorescent analysis confirmed that 2019-nCoV, having amino acid homology to SARS-CoV, might be able to use same human ACE2 receptor [angiotensin converting enzyme-2], which is highly expressed in the apical side of lungs epithelial cells in the alveolar space, that explains human to human transmission by infected droplets within the incubation period (6). So, Spike glycoprotein [S2] attachment to ACE2 receptor, is the basis of pathogenesis of transmission. Spike proteins S1 and S2 undergo sequential cleavage after host cell attachment. Apart from spike proteins, SARS-CoV also acquires other transmembrane proteins like RNA Polymerase, protease, helicase, and other accessory proteins, which are the target of drug therapy, but still under consideration (6). Even infected persons are used for randomized controlled trials to develop therapeutic strategies against SARS-CoV. The comparison study between SARS-CoV and SARS-CoV-2 by Angeletti *et al.*, elucidates the possibility of viral spike mutation, which promotes jumping to humans (14). But extensive data will necessitate the ultimate information underlying the pathogenesis.

Dysregulation of host cell immune response has been elaborately studied in adult severe COVID-19 patients with acute respiratory distress syndrome, which resembles SARS-CoV to a great extent (1). COVID-19 infects both upper and lower respiratory tract, more specifically ACE2 receptor present predominantly on epithelial cells of alveolar space. Alveolar macrophages and dendritic cells (below epithelium) confer innate immunity against virus till T-cell mediated adaptive immunity is necessitated, where CD4 T cell and CD8 T cells actively take part. The former can phagocytize apoptotic virus infected cells whereas latter activate antibody production to kill it. So, during infective period, definitive

lymphopenia (substantially reduced CD4 and CD8) was noted in severe COVID cases, which might be a crucial factor for assessment of disease severity and fatality (15). Moreover, data so far available, stipulate a "cytokine storm" in host due to excessive immune reaction by a viral infection resulting in acute respiratory syndrome. Various cytokines are identified to accomplish the pathogenesis such as: tumor necrosis factor [TNF- α], interleukin-1 [IL-1b], several interleukins(IL)[IL-2, IL-6, IL-7, IL-10], interferon gamma induced protein [IP-10], macrophage inflammatory protein [MIP-1A], granulocyte colony-stimulating factor [G-CSF], monocyte chemoattractant protein [MCP], ligand 3 [CCL-3] and many more (16, 17). Amongst, IL-6 and IL-10 take a protagonist role as a chemoattractant, assist in the differentiation of B-lymphocytes, and prompts acute phase protein synthesis. They accelerate the progression of the systemic inflammatory response, as evident from a large number of inflammatory cells in the lungs in severe COVID-19 patients. Thus, they seem to be used as a prognostic marker, capable of differentiating mild from severe cases (18). Suppression of inflammation will definitely influence viral clearance and can be implemented therapeutically to control many inflammatory diseases.

Mild-moderate-severe clinical manifestations

According to epidemiological data and clinical reports, manifestations of COVID-19 vary from mild-moderate to severe ARDS with multiorgan failure (19). Generally, symptoms appear after an average incubation period of 11 days [5-14days]. Mild, uncomplicated features of low fever, dry cough, sore throat, malaise, headache, and myalgia appear to be propitious in majority of patients. Atypical gastrointestinal symptoms like anorexia, nausea, and diarrhea are also seen. Respiratory symptoms with shortness of breath (tachypnea), if develop few days after early onset, suggest worsening of the condition (3). Fever with severe dyspnea and hypoxia with less than 90% oxygen saturation usually warrants severity of disease leading to ARDS, where clinical diagnosis and radiological imaging of chest (chest radiograph, computed tomography scan of lungs) are required to preclude complications like respiratory failure, sepsis and multiorgan failure in some cases (1). Echocardiography also helps to rule out cardiac failure and pulmonary origin of edema. Impoverished results could be observed in elderly persons (more than 65 years) and neonates due to their weak immunity. More so persons with comorbid conditions like diabetes mellitus, hypertension, COPD, CVD rapidly progress into critical complications such as ARDS, septic shock, metabolic acidosis, liver dysfunction, and death (1). But it is uncomprehensive

whether certain conditions like immunocompromised state, end stage renal disease, liver disease, and cancer increase the risk of fatality or not. Proximate observation can validate these case findings.

Laboratory finding and diagnosis

For the WHO suspected cases, Real time reverse transcription PCR [rtRT-PCR] of respiratory sample (upper respiratory: nasopharyngeal/ oropharyngeal swab in ambulatory patients and lower respiratory: expectorated sputum / bronchoalveolar lavage / endotracheal aspirate) remains the molecular test of choice for clinical diagnosis (9). Sometimes, the test tends to give false-positive and false-negative results. Therefore, test should be repeated in strong suspicion of cases with negative result. Even this test should be done before declaring a person COVID free after treatment. India, being a developing country, is facing a lot of challenges for diagnosis such as lack of well-equipped RNA based molecular laboratories, limited supply of kits and restrictive biosafety of testing facilities. That is the major reason of underestimation of true confirmed cases. Specific IgG antibody should be considered seriously for suspected cases to assess infectious conditions and also for community-based surveillance in India. Standard radiological imaging of chest has a critical role in diagnosis in advanced stage lungs involvement showing pneumonia and even pleural effusion. CT chest is the method of choice for evaluation of pneumonia with significant pulmonary changes like ground glass opacity, bilateral patchy consolidation, alveolar exudates (2). Biochemical and hematological parameters, indicative of disease severity and fatality include lymphopenia, increase levels of D-dimer, lactate dehydrogenase [LDH], C-reactive protein [CRP], liver enzymes, procalcitonin, ferritin and prolonged prothrombin time (20). That apart, abnormal findings suggestive of renal and cardiac injury may be noted. Cardiac Troponin I level is used clinically to rule out heart injury in critically ill patients. Cytokine storm associated with immune mediated inflammation can also imply high risk, which has already been discussed under pathogenesis. Elevated ILs and TNF- α are usually observed in critically ill patients.

Treatment and prevention

COVID-19 pandemic is the most formidable challenge to humanity. As of now, there is a lack of a specific and fixed set of antiviral medications. So symptomatic and supportive care is recommended. Treatment guidelines and treatment approaches differ between countries depending on disease severity. For mild patients, fever and cough management (antipyretics) should be taken care of at home along with good nutrition and counseling to maintain good hygiene. Moderate and severe COVID cases need to be hospitalized and kept under observation for

supportive care. Respiratory deterioration could be effectively managed by high flow nasal cannula oxygen therapy. Non-invasive and invasive mechanical ventilation may be obligatory to save a life in case of respiratory failure, not responding to oxygen therapy. Several interventional therapeutic options have been proposed and experimented with unclear potency and safety issues. WHO recommends empiric antiviral therapy, along with mechanical ventilation as per the severity of symptoms. Initially, broad spectrum antibiotics, nebulization, interferon-gamma, and antiviral remdesivir were explored in the patients (21). Remdesivir was successfully experimented previously during SARS-CoV and MERS-CoV (22). Out of many antivirals assessed [such as Ribavirin, Lopinavir, Ritonavir, Penciclovir], Remdesivir (inhibitor of RNA Polymerase) alone or with chloroquine can block viral replication inside the host and it is documented to be effective against pathogen (23). A recent in vitro study has documented its efficacy for both prophylactic and therapeutic purposes (24). Antiviral favipiravir has also shown effectiveness in clinical recovery. Chloroquine (CQ) and hydroxychloroquine (HCQ), used in malaria and autoimmune diseases respectively have been documented to be efficacious in vitro against 2019-nCoV by inhibiting the fusion of virus to cell membrane by modulating endosomal pH and by inhibiting replication (25). HCQ is a less toxic derivative of CQ but it is known to cause QT prolongation. Also, azithromycin which is frequently used along with HCQ, has shown to have pro-arrhythmic potential. Toxic effects of high dose of these drugs can be potentially life threatening. So randomized control trials are needed to clarify this aspect before implementation. HCQ prophylaxis has been advised only for healthcare workers coming in direct contact with confirmed cases, not for general population. Similarly, corticosteroids, though not recommended in any guidelines of WHO, are also a commonly used medication. It is thought to suppress inflammation but at the same time it hinders immune response which delays in viral RNA clearance. That apart, obvious side effects like hyperglycemia, hyponatremia, and hypokalemia should be monitored carefully (26). So attentive assessment of benefit versus risk should be done before use of corticosteroids clinically. No doubt, it is challenging to implement therapeutics without clarity on efficiency, safety, and well-being. At present, the need for effective treatment is imperative to stop the outbreak and to reduce mortality.

Recent therapeutic developments

1. Ivermectin: FDA approved broad spectrum antiparasitic agent which could reduce viral replication up to 5000-fold at 48 hours. Thus, it could act as potential therapeutic agent (27).

2. Plasma therapy: Brisk effect and fast recovery have been observed when convalescent plasma with a high titer of neutralizing antibodies from recovered patients are injected into infected individuals (28). This has been used based on the experience with the SARS epidemic during 2003 and H1N1 virus outbreak of 2009, where plasma therapy was used for treatment. But in India, it is still at an experimental stage (trial and research), after the clearance by Indian council of medical research [ICMR] to several states.
3. Monoclonal antibody: Therapeutic and prophylaxis effect of CR3022 monoclonal antibody has been recognized, which acts without affecting ACE2 receptor domain (29).
4. Immunomodulator therapy: IL-6 inhibitors like Tocilizumab, Sarilumab, and Siltuximab to reduce cytokine induced inflammation. Cytokine storm remains the proposed mechanism for ARDS. Clinical trials are registered and conducted in different countries (30) Baricitinib, janus kinase inhibitor used for Rheumatoid arthritis, are underway to prove its efficacy in COVID-19 (31).
5. Micronutrients: vitamin D deficiency may enhance the risk of COVID-19 severity. Potential immunomodulation by Vitamin D may be helpful for viral clearance at early stage of disease transmission, which ameliorates disease severity and influences disease outcome. That apart, vitamin C, vitamin A, selenium, zinc also play a vital role in modulating the risk and clinical course of COVID-19 (32).
6. Arsenic album: As suggested by ministry of AYUSH, Arsenic album 30 could be used as prophylactic agent if taken in empty stomach. That apart others like Tulsi leaves, *Agastya*, *Trikatu* and *Harityaki* also provide supporting evidences. Unani medicine have also been advised but lack robust evidences.

Vaccines

Amidst the bleakness of the pandemic, a safe and effective vaccine emerges as a ray of hope. It is the need of the hour and it is by far the best way to control the pandemic and to achieve pre-pandemic normalcy. As of now, no vaccine has been approved, although development is moving at an unprecedented speed across the world. Currently there are 11 vaccine candidates in the final phase of human trials globally. People all over India wait with bated breath for the vaccine to combat the spread of this ravaging disease. So far, there are 3 vaccine candidates in different phases of clinical trials in India. Indian researchers are seriously working on country's first indigenous coronavirus vaccine Covaxin, developed by Hyderabad based Bharat Biotech and ICMR-NIV [Indian council of medical research and national institute of virology] collaboration. Early findings of

phases-I clinical trials pave the way for second phase trials. That apart, Serum Institute Pune (Oxford University-AstraZeneca: Covidshield) and Zydus Cadila (DNA based vaccine ZyCoV-D) are the leading contestants in vaccine race in India. Even in the best-case scenario, vaccine is approved by the ends of 2020 or beginning of 2021, distribution and mass-immunization are going to be a daunting task.

Prevention

In the present scenario, prevention is the ongoing approach to curb the spread of COVID cases. Efficacious prevention needs swift action from the standpoint of public health strategies, which entail home isolation of suspected cases to control human contacts and droplet spread. Due to lack of definite treatment, following WHO recommended preventive strategies are targeted in the general population at community level such as: i] no direct contact with infected and symptomatic persons ii] following practice of hand hygiene like washing hands frequently with soap or use of alcohol based hand rub and not touching face, mouth, nose, eyes after handling with a contaminated object iii] use of surgical face mask for those with respiratory symptoms (not by healthy people) iv] social distancing and avoid crowded areas and postpone unnecessary travel to COVID-19 hit areas v] strict avoidance of public gatherings for immunocompromised and persons with comorbid conditions vi] maintenance of strict hygiene measures of inanimate surface vii] to ensure effective environmental cleaning (2). However, the necessity for health care workers is more looking at their huge health risks. Protection of health care workers is essential to restrain spread of infection among colleagues and to other patients. Personal protective equipment [PPE] such as N95 mask, protective gown, gloves, face shields, visors, and goggles, is required in hospital settings, where procedures like nasopharyngeal swab collection, endotracheal intubation, respiratory suctioning are performed. To date, hundreds of healthcare workers lost their lives battling this deadly virus. The major obstacle in prevention strategies lies in the mode of human to human transmission like i] transmission from an infected person without any noticeable symptoms (mild symptoms) ii] transmission from asymptomatic persons (during incubation period) iii] transmission from symptomatic persons for a prolonged period (not exactly known) iv] transmission from inanimate or insentient surfaces (lifeless objects in the environmental surrounding) v] transmission after disease remission(though rare) (11, 33). This unusual nature of coronavirus is certainly a matter of concern.

CONCLUSION

Several viral epidemics have been observed in the last twenty years such as SARS-CoV in 2002, H1N1 Influenza in 2009, and MERS-CoV in 2012. Recent

COVID-19 pandemic is declared as a public health emergency of international concern. Lives of millions of people have changed radically in the past few months. It is worth mentioning here that it is much more than a health crisis because of the unprecedented socio-economic crisis. The global economy is heading towards a deep recession. As per the current evidence, it is difficult to assess the unpredictable pathway of this virus. More importantly, it is tough to assess how this will impact our lives in the future. In the present scenario, the greatest challenge to build resilience is to reduce virus spread as there are no potential therapeutic strategies available so far. Till date, COVID situation in India has been tackled by containment course of action like quarantine, isolation of infected persons, contact tracing. But with the current shoot up in the number of cases, priority should be on community mitigation by social distancing and minimizing unnecessary exposure to vulnerable populations. ICMR-NIV has indulged in extensive research to appraise the condition of human-human transmission and pathogenic mechanisms. Spike glycoprotein target therapy as well as RNA Polymerase target therapy are being evaluated to come up with prospective therapeutics against COVID-19. In the midst of the pandemic and in the absence of any efficacious therapeutics, COVID-19 vaccines are on trial for its safety and efficacy, where community engagement and preparedness should be addressed properly. More so strict endeavors should be undertaken to anticipate and to avert upcoming viral epidemics.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., *et al.*, Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *Lancet*. 2020; 395(10223): 497-506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
2. Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S.C., Di Napoli, R., Evaluation and treatment of Coronavirus (COVID 19) [updated 2020 July 4]. 2020; In: StatPearls [Internet]. Treasure Island (FL): Statpearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK554776/>
3. Harpan, H., Itoh, N., Yufika, A., Winardi, W., Keam, S., Te, H., Megawati, D., *et al.*, Coronavirus disease 2019 (COVID-19): A Literature review. *Journal of Infection and Public Health*. 2020; 5(13): 667-673. <https://doi.org/10.1016/j.jiph.2020.03.019>
4. Coronavirus outbreak. Available at: <http://www.wordometers.info/coronavirus/>.
5. Paules, C. I., Martson, H. D., Fauci, A. S., Coronavirus infection: more than just the common cold. *JAMA*. 2020; 323(8): 707-8. <https://doi.org/10.1001/jama.2020.0757>
6. Wu, F., Zha, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., *et al.*, A new coronavirus associated with human respiratory disease in China. *Nature*. 2020; 579(7798): 265-269. <https://doi.org/10.1038/s41586-020-2008-3>
7. Zhou, P., Yang, X., Wang, X., Hu, B., Zhang, L., Zhang, W., *et al.*, A Pneumonia outbreak associated with a new

- coronavirus of probably bat origin. *Nature*. 2020; 579: 270-273. <https://doi.org/10.1038/s41586-020-2012-7>
8. Hu, D., Zhu, C., Ai, L., He, T., Wang, Y., Ye, F., *et al.*, Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bat. *Emerge Microbe Infect.* 2018; 7: 154. <https://doi.org/10.1038/s41426-018-0155-5>
9. Wang, C., Horby, P. W., Hayden, F. G., Gao, G. F., A novel coronavirus outbreak of global health concern. *The Lancet*. 2020; 395(10223): 470-473. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)
10. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., *et al.*, Early transmission dynamics in Wuhan, China, of novel coronavirus infected pneumonia. *N Eng J Med*. 2020; 382: 1199-1207. <https://doi.org/10.1056/NEJMoa2001316>
11. Wei, W. E., Li, Z., Chiew, C. J., Young, S. E., Toh, M. P., Lee, V. J., Presymptomatic transmission of SARS-CoV-2, Singapore. *Morb Mortality Wkly Report*. 2020; 69(14): 411-415.
12. Hindson, J., COVID-19: Feco-oral transmission. *Nat bRev Gastroenterol Hepatol*. 23020; 104: 4-5. <https://doi.org/10.1038/s41575-020-0295-7>
13. Wall, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., Veesler, D., Structure, function, and antigenicity of SARS-CoV-2 glycoprotein. *Cell*. 2020; 16: 281-292. <https://doi.org/10.1016/j.cell.2020.02.058>
14. Angeletti, S., Benvenuto, D., Bianchi, M., Giovanetti, M., Pascarella, S., Ciccozzi, M., COVID-2019: The role of the nsp2 and nsp3 in its pathogenesis. *Jour of Med Virology*. 2020; 92: 584-588. <https://doi.org/10.1002/jmv.25719>
15. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., *et al.*, Pathological findings of COVID-19 associated with Acute Respiratory Distress Syndrome. *Lancet Respir Med*. 2020; 8(4): 420-422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
16. Conti, P., Ronconi, G., Caraffa, A., Gallenga, C. E., Ross, R., Frydas, I., *et al.*, Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19(COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regulators and Homeostatic Agent*. 2020; 14: 34(2). <https://doi.org/10.23812/CONTI-E>
17. Costela-Ruiz, V. J., Illescas-Montes, R., Puerta-Puerta, J. M., Ruiz, C., Melguizo-Rodríguez, L., SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev*. 2020; 54: 62-75. <https://doi.org/10.1016/j.cytogfr.2020.06.001>
18. Velavan, T. P., Meyer, C., Mild versus severe COVID-19: Laboratory markers. *Int J Infect Dis*. 2020; 95: 304-307. <https://doi.org/10.1016/j.ijid.2020.04.061>
19. Wu, Z., McGoogan, J.M., Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13): 1239-42. <https://doi.org/10.1001/jama.2020.2648>
20. Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z., Harky, A., The role of biomarkers in the diagnosis of COVID-19-A Systematic Review. *Life Sci*. 2020; 254: 117788. <https://doi.org/10.1016/j.lfs.2020.117788>
21. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., *et al.*, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus(2019-nCoV) in vitro. *Cell Res*. 2020; 30: 269-271. <https://doi.org/10.1038/s41422-020-0282-0>
22. Sheahan, T. P., Sims, A. C., Graham, R. L., Menachery, V. D., Gralinski, L. E., Case, J. B., *et al.*, Broad spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronavirus. *Sci Transl Med*. 2017; 9(396): eaa13653. <https://doi.org/10.1126/scitranslmed.aa13653>
23. Gordon, C. J., Tchesnokov, E. P., Feng, J. Y., Porter, D. P., Götte, M., The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J. Biol. Chem*. 2020; 295(15): 4773-4779. <https://doi.org/10.1074/jbc.AC120.013056>
24. de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., *et al.*, Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc. Natl. Acad. Sci. USA*. 2020; 117(12): 6771-6776. <https://doi.org/10.1073/pnas.1922083117>
25. Gendrot, M., Javelle, E., Clerc, A., Savini, H., Pradines, B., Chloroquine as a prophylactic agent against COVID-19. *Int J Antimicrob Agent*. 2020; 55(6): 105980. <https://doi.org/10.1016/j.ijantimicag.2020.105980>
26. Tobaigy, M., Qashqary, M., Al-Dahery, S., Mujallad, A., Hershan, A. A., Kamal, M. A., Helmi, N., Therapeutic management of patients with COVID-19: A systematic review. *Infection Prevention in Practice*. 2020; 2(3): 100061. <https://doi.org/10.1016/j.infpip.2020.100061>
27. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., Wagstaff, K.M., FDA approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020; 178: 104787. <https://doi.org/10.1016/j.antiviral.2020.104787>
28. Derebail, V. K., Falk, R. J., ANCA-associated vasculitis-refining therapy with plasma exchange and glucocorticoid therapy. *N Eng J Med*. 2020; 382(7): 671-673. <https://doi.org/10.1056/NEJMe1917490>
29. Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z., *et al.*, Potent binding of 2019-novel coronavirus spike protein by a SARS coronavirus specific human monoclonal antibody. *Emerg Microbes Infect.* 2020; 9(1): 382-385. <https://doi.org/10.1080/22221751.2020.1729069>
30. Atal, S., Fatima, Z., IL-6 inhibitors in the treatment of serious COVID-19: A promising therapy. *Pharmaceut Med*. 2020; 13: 1-9. <https://doi.org/10.1007/s40290-020-00342-z>
31. Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., *et al.*, Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020; 395: e30-e31. [https://doi.org/10.1016/s0140-6736\(20\)30304-4](https://doi.org/10.1016/s0140-6736(20)30304-4)
32. Chowdhury, A. I., Role and effects of micronutrients supplementation in immune system and SARS-CoV-2 (COVID-19). *Asian Journal of Immunology*. 2020; 4(2): 47-55. <https://www.journalaji.com/index.php/AJI/article/view/30133>
33. van Doremalen, N., Bushmaker, T., Morris, D. H., Holbrook, M. G., Gamble, A., Williamson, B. N., *et al.*, Aerosol and surface stability of SARS-CoV-2 as compared to SARS-CoV-1. *N Eng J Med*. 2020; 382(16): 1564-67. <https://doi.org/10.1056/NEJMc2004973>