



THE COVID-19 PANDEMIC- A COMPREHENSIVE INSIGHT ON THE RECENT UPDATES.

Anu Sharma^{1*}, Ravi P Sharma², Sonal Agarwal³, Manushri Sharma⁴, Amardeep Pathak⁵, Govind Mishra⁶

¹M.D. Microbiology, Dr V.M. Government Medical College, Solapur, Maharashtra.

²Post Graduate Student, Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur

³Post Graduate Student, Department of Microbiology, Dr V.M. Government Medical College, Solapur, Maharashtra

⁴Associate Consultant Biochemistry, Clinical Laboratory Services, Sir Ganga Ram Hospital, New Delhi.

⁵Consultant and Head Transfusion Medicine Rajiv Gandhi Cancer Institute and Research Centre, New Delhi.

⁶M.D. Pharmacology, All India Institute of Medical Sciences, Jodhpur

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Corresponding author: Dr. Anu Sharma

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Abstract:

Currently world is facing a pandemic caused by novel corona virus (SARS –CoV2) which causes a highly contagious infection affecting most commonly lungs and results in an array of clinical symptoms ranging from asymptomatic state to acute respiratory distress syndrome and may even lead to multi organ dysfunction. Although pulmonary manifestations are common in patient but there are various extra pulmonary manifestations too which cannot be overlooked. The infection spread via respiratory droplets or from the surfaces where these droplets may get deposited and fomites of the infected person. The incubation period of virus is around 2- 14 days. The diagnostic modalities include Reverse transcriptase real time PCR (rtqPCR) which is gold standard method for diagnosis of the infection using oro-pharyngeal or nasopharyngeal swabs from the patients. Serological testing for antigen and antibody detection is also available now. The Indian Council of Medical Research (ICMR) has validated and approved serological kits for the same, rapid diagnostic test (RDT) for antigen detection is widely used now; however antibody detection IgM/IgG by ELISA is strictly confined for epidemiological purpose and testing in the containment zone. Clinical symptoms along with imaging technique, increased biomarkers and other lab parameters all aid in the diagnosis of the infection. Till date no specific treatment or vaccine is available for the infection so management of patient is supportive and symptomatic. Major pharmaceutical companies world-wide are exploring options for new vaccine development. Many older drugs with known safety profile are repurposed and seen for their efficacy in COVID-19 patients. A wide range of technology platforms are being evaluated for vaccine development at an unprecedented scale and speed. This review highlights comprehensively on all the recent updates about COVID-19.

Keywords: SARS-CoV-2 (Severe acute respiratory syndrome-Coronavirus-2), PCR (Polymerase chain reaction), rtqPCR (Reverse transcriptase real time PCR), ICMR (The Indian Council of Medical Research), COVID-19 (Coronavirus disease), ELISA (Enzyme linked immuno- sorbent assay), RDT (Rapid diagnostic test).

Introduction:

Coronaviruses are positive sense single stranded RNA viruses with a diameter of about 80-120 nm¹. It belongs to the Coronaviridae family whose members have spike like projections on the surface of the virus, giving it the appearance of a crown as seen under an electron microscope². The Coronaviridae family has two subfamilies namely Letovirinae and orthocoronavirinae. Orthocoronavirinae subfamily has four genus alpha, beta, gamma and delta Coronavirus. Alpha and beta Coronaviruses are seen to infect only mammals while gamma and delta coronaviruses primarily infect birds and in rare occasion it can infect mammals too³. Six coronaviruses are known to trigger infection in humans prior to SARS – CoV-2, including SARS-CoV or SARS-CoV-1, MERS – CoV that caused outbreaks in 2002-03 and 2012, respectively⁴. SARS-CoV, MERS-CoV, and SARS -COV-2 all belong to the betacoronavirus genus⁵. Most common coronaviruses that circulate among human population with

mild respiratory illness include 229E, NL63 (alphacoronavirus) and HKU1 and OC 43 (betacoronavirus)² The SARS-COV -2 genetic sequence was published on 11 January 2020⁶. The genome sequence homology indicates that SARS-CoV -2 has 88% similarity to the bat coronavirus (MG 7729330), while similarity between SARS-COV -2 and SARS-CoV was found to be 79% while 50% similarity between SARS-CoV-2 and MERS-CoV was observed. The genomic homology studies clearly suggests that the source of SARS -COV -2 is bat with yet unknown intermediate host which must have acted as an amplifier⁷.

History

Coronaviruses in the past have caused outbreaks, two outbreaks of SARS-CoV has occurred in the last twenty years, where the cross-over of animal beta coronaviruses to humans culminated in an outbreak which later spread to other countries. In late 2002 SARS-CoV outbreak was reported from Guangdong province in China where bats were found to be the natural reservoir of the virus and was

transferred to humans by palm civet cats which acted as intermediate host. Another outbreak that occurred in Saudi Arabia in the year 2012, where bats were found as the reservoir of the virus and camel was the intermediate host, later came to be known as MERS-CoV (Middle East Coronavirus Respiratory Syndrome).

In December 2019, few cases of pneumonia of unknown origin were reported from Wuhan, Hubei Province, China (Public Republic of China) by examining patients' respiratory samples on January 7, 2020, the pathogen was identified as a novel Coronavirus that differed from previous known Coronaviruses (SARS-CoV and MERS-CoV) that had resulted in outbreak in the past. Epidemiological investigation and source tracing showed that there was link between the SARS - COV -2 with Wuhan Huanan seafood market (wet market) which was shut down and later sanitized. First fatal case of SARS-CoV-2 was reported on January 11, 2020. World Health Organisation (WHO) declared it as Public health problem of International Concern on January 30, 2020 and officially declared it as pandemic on March 11, 2020. At the time of this review (July 23, 2020) world-wide total cases of COVID-19 were 15,379,943 with 630,313 deaths. In India total cases with COVID-19 were 1239,684 with 29,890 deaths¹¹

Etiopathogenesis

SARS-CoV -2 is a positive sense single stranded RNA virus with multiple open reading frames (ORF's) encoding for various structural and non-structural proteins. Spikes present on the surface of virus recognise the host ACE- 2 (angiotensin converting enzyme-2) receptors. These receptors are seen in lungs but evidence suggest that they are expressed in other organs also, the interaction between viral spikes and ACE-2 receptor enables viral fusion and entry into the host cell¹². Viral RNA contains 5'cap and 3' poly tail that allows expression of enzyme replicase, this enzyme is encoded by major part of the genome. The remaining part of the genome encodes for other structural and non-structural proteins. The non-structural proteins encoded by the help of its two poly proteins and viral protease. Later there is assembly of non - structural proteins to form replicase transcriptase complex (RTC) in the host cytoplasm and new viral genome is synthesised. Structural proteins like S(Spike), M (Matrix) E(Envelope) proteins move to endoplasmic reticulum and are processed in Golgi apparatus after final assembly they are exocytose in an vesicle to the host cell surface from where they disseminate to other sites². Spike (S) proteins have two sub units S1 and S2. Of which S1 is specific to SARS-CoV-2 while S2 shares epitopes with other Coronaviruses. For effective SARS - CoV -2 interaction with

ACE-2 receptors priming of spike proteins with cellular serine protease TMRSS 2 / Furin is required .The

mechanism of receptor recognition of SARS-CoV-2 is similar to other coronaviruses like SARS - CoV and MERS-CoV. The ACE-2 receptors are found in abundance in respiratory tract, gastrointestinal tract, cardiovascular system, renal system and central nervous system. Due to wide spread ACE-2 receptor expression in various organs the disease has pulmonary as well as extra pulmonary manifestations. Studies have shown that SARS-COV2 binds with ACE 2 receptors with tenfold higher affinity than SARS -COV which explains the high transmissibility potential of SARS - COV -2¹³⁻¹⁵.

Transmission of SARS - COV -2 is most commonly by droplets and close contact. Infected droplets may deposit on surfaces where virus can remain viable for days and can effectively transmit infection. Surface disinfection using 1-5% hypochlorite is seen to kill the virus effectively. Studies have shown that high viral load is seen in the nasal cavity as compared to other parts of the body thus favouring droplet transmission¹⁶. All age are susceptible for the infection however elderly people with co- morbidities are more prone to develop severe diseases and may even lead to death. The case fatality rate (CFR) is age dependent. It is higher in elderly male. Overall CFR is 1-3%².

Clinical Manifestation

SARS - COV -2 most commonly affects the pulmonary system, symptoms are varied ranging from asymptomatic cases to acute respiratory distress syndrome (ARDS)¹. SARS - COV -2 may also cause significant extra pulmonary manifestations which are enlisted below.

Table 1: Various Extra pulmonary Manifestations in COVID -19 patients¹⁶.

System involved	Clinical Manifestations
Blood and other Coagulation Profile	Lymphopenia, Leucocytosis, Thrombocytopenia. Increase in inflammatory markers like Erythrocyte Sedimentation Rate, C-Reactive Protein, Ferritin, IL-6, Lactate dehydrogenase. Increase in coagulation indices like increase D- dimer, fibrinogen, Prolong Partial Thromboplastin time (PTT) and Prothrombin time (PT).
Gastro Intestinal system	Nausea, Vomiting Diarrhoea. Elevated Hepatic Transaminases, Elevated Bilirubin and Low Serum Albumin levels
Renal system	Acute kidney injury Electrolyte Imbalance like Hyperkalemia Hypernatremia, Proteinuria, Hematuria Metabolic acidosis
Endocrine System	Hyperglycemia, Ketoacidosis.
Cardiovascular system	Myocardial ischemia, Myocarditis, Arrhythmia Cardiomyopathy, Cardiogenic shock
Central nervous system	Headache, dizziness, Anosmia, Ageusia, Anorexia, Myalgias, Fatigue, Stroke, Encephalopathy, Encephalitis, Guillain Barre syndrome
Skin	Erythematous rashes, Urticaria, Acro-Cutaneous Lesions

The clinical manifestation caused by SARS-CoV -2 is primarily by the direct action of the virus, virus induced endothelial cell damage causes endothelial inflammation and leads to activation of thrombin which causes conversion of fibrinogen to fibrin, thus favouring micro thrombi formation in vessels. In addition to activation of the coagulation cascade, activation of complement system also facilitates the release of pro-inflammatory cytokines which later lead to a condition known as cytokines storm in the patients and result in elevation of serum inflammatory markers like C-reactive protein, Erythrocyte sedimentation rate, D-dimer, fibrinogen, ferritin, lactate dehydrogenase and IL -6. Deregulation of renin-angiotensin-aldosterone-system also affects the blood pressure, fluid electrolyte balance and systemic vascular resistance. All this leads to worsening of patient's symptoms and may even result in death.

Diagnosis

The detection of viral RNA is done by reverse transcription real time polymerase chain reaction or (rtqPCR) using patient's oro-pharyngeal or nasopharyngeal swab. It is the gold standard method for diagnosis of SARS-COV-2. Target for molecular assay for initial screening is Envelope (E) gene, while confirmation is done by detection of RNA dependent RNA Polymerase (rdrp) gene, Open Reading Frame (ORF 1a and 1b) and Nucleoprotein (N) gene. Rapid diagnostic test (RDT) using immuno chromatography principle for antigen detection is also available which detects Nucleoprotein (N) or Spike (S) antigen in patient's sample. If the test result using RDT is positive it has to be reported as true positive, however if the test results are negative by RDT in a symptomatic patient, the confirmation by molecular assay is mandatory. In case of negative report in an asymptomatic patient, it has to be reported as it is. Antibody detection IgM/IgG antibodies against Nucleoprotein (N) or Spike (S) antigen by ELISA kits are also available but their use is confined for epidemiological purpose and in containment zone only¹⁷. Elevated biomarkers which indicate release of pro inflammatory cytokine help in the prognosis as well as management of the patient. Imaging technique like Computerized tomography (CT) scan is very useful in diagnosis of cases when clinical suspicion is strong and laboratory reports are awaited or negative¹⁶. Recently Cartridge based nucleic acid amplification test (CBNAAT) and TRUNAAT a chip based real time PCR for SARS-CoV-2 is also approved for diagnosis of SARS-COV-2. Other newer platforms like Reverse transcriptase-Loop mediated isothermal nucleic acid amplification technique (RT-LAMP) , CRISPER based SHERLOCK (Specific high sensitivity enzymatic reporter unlocking) technique and sequencing techniques like SHERRY (Sequencing Hetero RNA-DNA-Hybrid) will be helpful for rapid diagnosis of SARS-CoV-2.

But further studies are needed in this respect as once proved these technology will be helpful for rapid diagnosis^{18,19}.

Treatment of SARS-CoV-217

As of now no approved treatment or vaccination is available, therefore supportive and symptomatic treatment is given to the patients. Currently many drugs are explored for their efficacy in treatment of COVID-19. Some known drugs like Hydroxy-chloroquine (HCQ), Ivermectin are repurposed and given to COVID-19 patients as there safety profile is known. Antiviral like Remdesivir /Fabipiravir/ Lopinavir/ Ritonavir are also tried in COVID-19 patients. With evidence of increase in biomarkers, CT scan findings suggestive of ground glass opacity, consolidation, sub-pleural thickening and worsening of oxygen saturation. Use of steroids, monoclonal antibody like Tocilizumab along with ventilator support is advocated as these drugs may help in decrease in release of cytokines and will alleviate the symptoms of the patients.

Other add on drugs advised includes Vitamin C, Zinc , Vitamin D, Low Molecular Weight Heparin (LMWH) along with CARP protocol (Covid Awake Respiratory Prone Protocol) and limb physiotherapy to prevent deep vein thrombosis. As the treatment is supportive and symptomatic. Preventive measures like maintenance of hand hygiene, following cough etiquettes, maintaining social distancing and use personal protective gear like masks is cornerstone in prevention of infection and it will help in breaking the transmission chain.

Vaccine development and Challenges

At this point of time no vaccine is available for the treatment of SARS-CoV-2 .Global efforts involving governments across the world, major pharmaceutical companies are exploring treatment options and developing potential vaccine candidates at an unprecedented scale and speed. Appropriate drug therapy and vaccine for prophylaxis is the need of the hour. Currently there are seven main platforms explored for vaccine development. These platforms include- Nucleic acid platform- DNA & RNA vaccines, Subunit/ Protein based vaccine, viral vector vaccine, Inactivated vaccine, Live attenuated vaccine and others which includes all other platforms that are currently explored like Virus like particle (VLP's), use of killed non – CoV-2 (killed rabies virus) or live modified horse pox virus and repurposed vaccines like BCG, MMR, OPV 20 . But development of COVID-19 vaccine in such short span of time comes with lots of challenges like many companies globally claim that vaccine will be marketed soon but various factors have to be taken in consideration before manufacture of vaccine which includes safety and efficacy of the vaccine ^{21,22}. Secondly once the vaccine is approved there is a need of large scale production of

vaccine, the time period required to meet such enormous demand of vaccine is a challenging task²³. Another important factor that has to be considered is that although Antibody dependent enhancement (ADE) phenomenon has not been seen in SARS-CoV-2 pre-clinical studies, but still should be under consideration as it is seen in other viral infections like Dengue, Zika and influenza virus¹². Other factors like age and co-morbidities are also to be kept in mind while developing a vaccine, as studies have shown that with ageing and co-morbidities lowers the effectiveness of vaccination²⁴. Lastly the periods till which vaccine will provide protection are factors that need further evaluation.

Table 2: Vaccines under Clinical trials²⁵

S.NO	Candidate	Sponsor	Clinical Phase	Type of Vaccine
1	AZD1222	Astrazeneca/ University of Oxford	Phase 2 & 3	Adenovirus vector vaccine
2	m-RNA 1273	Moderna therapeutics	Phase-2	m-RNA vaccine
3	BNT-162	Pfizer/ BioNTech	Phase 1 & 2	m-RNA Vaccine
4	Inactivated Vaccine	Wuhan Institute of Biological Products/ Sinopharm	Phase 1 & 2	Inactivated vaccine
5	BBIBP-CorV	Beijing Institute of Biological Products/ Sinopharm	Phase 1 & 2	Inactivated vaccine
6	A Ad5-nCoV	Can Sino Biologics	Phase -1	Adenovirus vaccine
7	INO-4800	Inovio Pharma	Phase-1	DNA Vaccine
8	BBV152 (Covaxin)	Bharat Biotech International Ltd. Indian council of Medical Research	Phase-1	Whole virion inactivated SARS-CoV-2 vaccine

(Source website- <http://www.clinicaltrials.gov> the vaccine candidate included in the above table are the most promising candidates although at present thirty one potential candidates are under clinical trials)

Conclusion

Novel coronavirus (SARS-COV-2) poses major threat to global public health. Exponential rise in COVID -19 cases have lead Government of various countries to impose lockdown, which has given a harsh blow to global economy, however we all must be optimistic that given the speed and scale of research work, funding by Govt.as well as by non-government organizations (NGO's) and the efforts of major pharmaceutical companies, vaccine for SARS-COV-2 will be available soon. At present the treatment of COVID-19 patients is symptomatic and supportive therefore prevention is important to avoid transmission of the infection.

References

- Jain N, Choudhury A, Sharma J, Kumar V, De D, Tiwari R. A review of novel Coronavirus infection (Coronavirus disease-19). *Glob J Transfus.Med* 2020;5:22-6.
- Fatima Amanat, Florian Krammer. Sars-CoV-2 Vaccines: Status Report. <http://doi.org/10.1016/j.immuni.2020.03.007>.
- Cui.J, Li. F, Shi Z.L. (2019) origin and evolution of pathogenic Coronaviruses. *Nat. Rev. Microbiol.* 17,181-192.
- De Wit. E, Van Doremalen, N.< Falzarano D., Munster V.J. (2016). SARS and MERS: Recent insights in to emerging Coronaviruses. *Nat. Rev . Microbiol.* 14,523-534. Doi: 10.1038/nrmicro.2016.81.
- Zhu N. Zhang D, Wang W, Li X., Yang B, Song J et al. A novel Coronavirus from patients with pneumonia in China 2019. *N. Engl. J. Med* 2020;382(8):727-33.
- Tung Thanh Le, Zacharias Andreadakis, Arun Kumar, Raul Gomez Roman, Stig Tollefsen, Melanie Saville, Stephen Mayhew. The COVID-19 Vaccine development Landscape. *Nature Reviews.* May 2020; 19:305-306. www.nature.com/nrd
- Wu A, Peng Y, Huang B, Ding X, Wang X., Niu P et al. Genome composition and divergence of the novel Coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 2020;27(3):325-8.
- 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, China. *Lancet* 2020;395:497-506.
- Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A.et al.(2020).World health organization declares global emergency: A Review of the 2019 novel Coronavirus(COVID-19). *Int J. Surg.*76,71-76.doi: 10.1016/j.ijssu.2020.02.034.
- <http://www.who.int>
- <http://worldometer.com>
- Fehr A.R., Perlman S. (2015). Coronaviruses: an overview of their replication and pathogenesis. *Methods. Mol. Biol.*1282,1-23.
- Wrapp, D et al. Cryo-EM Structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367,1260-1263 (2020).
- Wang Q et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE-2 cells. 181,894-904e9 (2020).
- Lei, C et al. Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE-2-Ig. *Nat. Commun.*11,2070 (2020).
- Aakriti Gupta, Mahesh V. Madhavan, Kartik Sehgal et al. Extra pulmonary manifestations of COVID-19. <http://doi.org/10.1038/s41591-020-0968-3>
- <http://www.mohfw.gov.in>
- Zhang F, Omar Abudayyeh O, Gootenberg J.S. [http://www.broadinstitute.org/files/publications/special/COVID-19 2020 detection](http://www.broadinstitute.org/files/publications/special/COVID-19%2020%20detection).

19. Di L, Fu Y, Sun Y, Li J, Liu L, Yao J et al. RNA sequencing by target segmentation of RNA/DNA hybrids. *Proc. Natl. Acad. Sci. USA* 2020;117:2886-93.
20. Thanh Le T, Andreadakis Z, Kumar a, Gomez Roman R, Tollefsen S, Saville M and Mayhew S. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*: Apr9,2020 (Epub ahead of print)
21. Daniela Calina, Anca Oana Docea, Demetrios Petrakis, Alex m. Egorov, Aydar A. Ishmukhametov, Alexandr G. Gabibov, Michael. I. Shtilman, Ronald Kostoff, Felix Carvalho, Marco Vinceti, Demetrios A Spandos and Aristidis Tsatsakis. Towards effective COVID-19 Vaccines: Updates, Perspectives and Challenges (Review). *Int. J. Mol Med*;46:3-16,2020. Doi:10.3892/ijmm.2020.4596.
22. Tetro JA: Is COVID-19 receiving ADE from other Coronaviruses? *Microbes Infect*22:72-73,2020.
23. Lord JM: The effect of ageing of the immune system on vaccination response. *Hum Vaccin Immunother* 9:1364-1367,2013.
24. Boda D, Docea AO, Calina D, Ilie MA, Caruntu C, Zurac S, Neagu M, Constantin C, Brainsteanu DE, Voiculescu V et al: Human Papilloma Virus: Apprehending the Link with carcinogenesis and unveiling new research avenues (Review). *Int J Oncol* 52: 637-655,2018.
25. <http://www.clinicaltrials.gov>