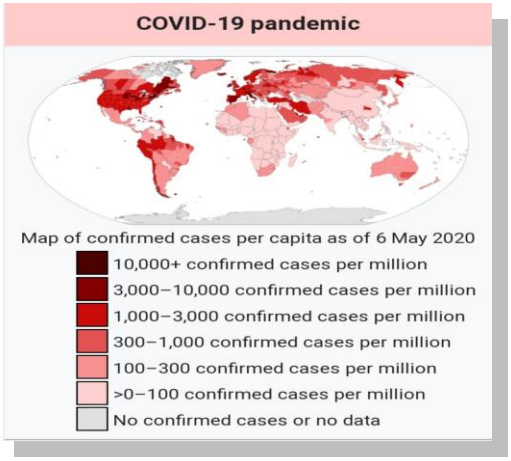
OPEN ACCESS INTERNATIONAL JOURNAL OF SCIENCE & ENGINEERING

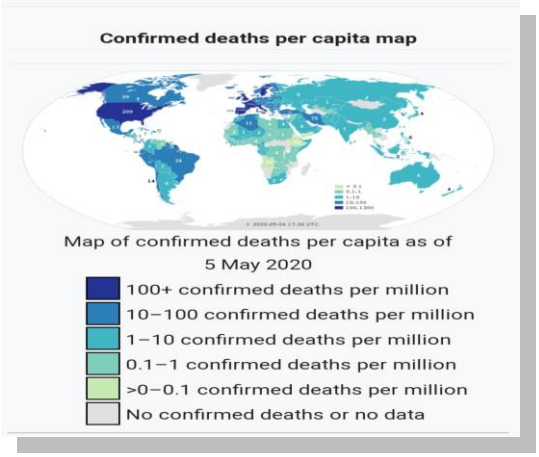
PANDEMIC WHICH CREATED HAVOC IN WORLD: COVID19

Ashwini A Mankar[1] and Vijay S Harode[2]

[1]Assistant Professor, Department of Biotechnology, Kamla Nehru Mahavidyalaya, Nagpur (INDIA)
[2]Assistant Professor, Department of Biotechnology, Kamla Nehru Mahavidyalaya, Nagpur (INDIA)
mankarashwini3@gmail.com, vijayharode29@gmail.com

Abstract: ***According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. The COVID-19 pandemic, also known as the coronavirus pandemic, is an ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak was identified in Wuhan, China, in December 2019. The World Health Organization declared the outbreak a Public Health Emergency of International Concern on 30 January, and a pandemic on 11 March. It is also named as Severe Pneumonia with Novel Pathogens on January 15, 2019 by the Taiwan CDC, the Ministry of Health and is a notifiable communicable disease of the fifth category. COVID-19 is a potential zoonotic disease with low to moderate (estimated 2%–5%) mortality rate. Person-to-person transmission may occur through droplet or contact transmission and if there is a lack of stringent infection control or if no proper personal protective equipment available, it may jeopardize the first-line healthcare workers. Currently, there is no definite treatment for COVID-19 although some drugs are under investigation As of 6 May 2020, more than 3.66 million cases of COVID-19 have been reported in over 187 countries and territories, resulting in more than 257,000 deaths. More than 1.19 million people have recovered.***





---------- ∴∴∴ ----------

INTRODUCTION

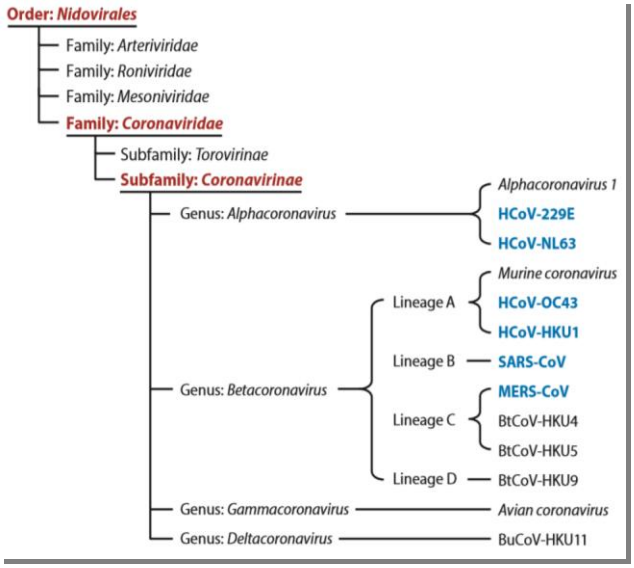
In a timeline that reaches the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family. The CoVs have

become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species and nucleocapsid of helical symmetry.[Cherry et. al. (2017)] This is wrapped in a icosahedral protein shell.["Chapter 24 - Coronaviridae". Fenner's Veterinary Virology (Fifth ed.) (2017)]The genome size of coronavirus ranges from approximately 26 to 32 kilobases , one of the largest RNA Viruses.**[**Woo et. al. (2010)] They have characteristic club-shaped spikes that project from their surface, which in electron micrographs create an image reminiscent of the solar corona, because of which the name is derived i.e "CORONAVIRUS".[Almeida et al. (1968)]

ETIOLOGY

The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus(betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages.[Hui et al (2019).Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources deltaCoVs and gammaCoVs.

The classification of Coronavirus is as following:



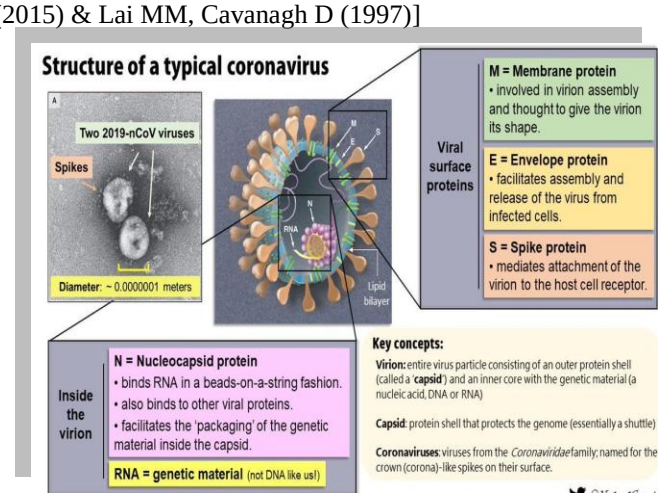
HISTORY

The first coronavirus was isolated in 1937. Some cause illness in people and others circulate among other animals, including camels, cats and bats. Since its discovery, related coronaviruses have been found to infect cattle, pigs, horses, turkeys, cats, dogs, rats, and mice. The first human coronavirus was cultured in the 1960s from nasal cavities of people with the common cold.

VIROLOGY:

Structure

Coronaviruses are large, mostly spherical, sometimes pleomorphic (changeable in shape), particles with bulbous surface projections. [Neuman et. al. (2006)] The average diameter of the virus particles is around 125 nm (.125 μm). The diameter of the envelope is 85 nm and the spikes are 20 nm long. The envelope of the virus in electron micrographs appears as a distinct pair of electron-dense shells (shells that are relatively opaque to the electron beam used to scan the virus particles . [Fehr AR, Perlman S (2015) & Lai MM, Cavanagh D (1997)]



The viral envelope consists of a lipid bilayer, in which the membrane (M), envelope (E) and spike (S) structural proteins are anchored. [Cavanagh et. al (2001)] The ratio of E:S:M in the lipid bilayer is approximately 1:20:300. [Neuman et. al. (2011)] On average a coronavirus particle has 74 surface spikes.[Chang et. al. (2014)]

The coronavirus surface spikes are homotrimers of the S protein, which is composed of an S1 and S2 subunit. The homotrimeric S protein is a class I fusion protein which mediates the receptor binding and membrane fusion between the virus and host cell. The S1 subunit forms the head of the spike and has the receptor binding domain (RBD). The S2 subunit forms the stem which anchors the spike in the viral envelope and on protease activation enables fusion. The E and M protein are important in forming the viral envelope and maintaining its structural shape.[Lai MM, Cavanagh D (1997)]

Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation.[Lai MM, Cavanagh D (1997)& Neuman et. al.

(2011)]The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell.[Snijder et. al. (2003)]

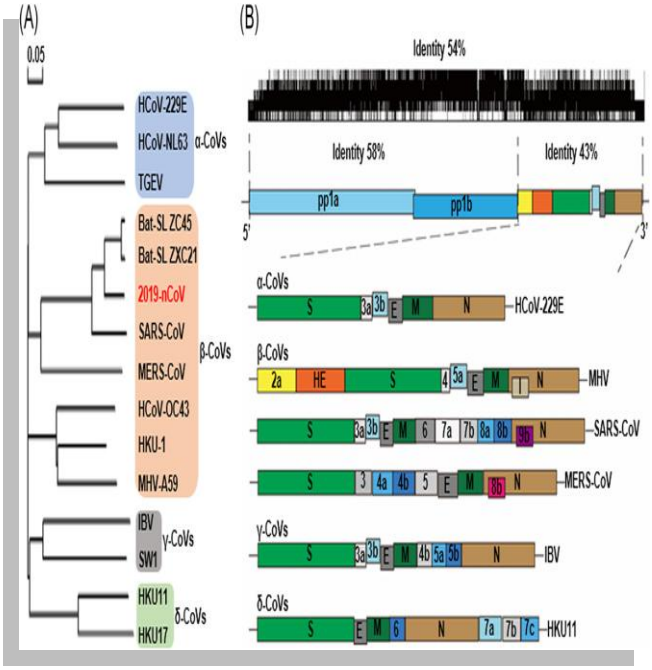
Genome

Coronaviruses contain a positive-sense, single-stranded RNA genome. The genome size for coronaviruses ranges from 26.4 to 31.7 kilobases. **[**Woo et. al. (2010)] The genome size is one of the largest among RNA viruses. The genome has a 5′ methylated cap and a 3′ polyadenylated tail. [Lai MM, Cavanagh D (1997)]

The genome organization for a coronavirus is 5′-leader-UTR-replicase/transcriptase-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail. The open reading frames 1a and 1b, which occupy the first two-thirds of the genome, encode the replicase/transcriptase polyprotein. The replicase/transcriptase polyprotein self cleaves to form nonstructural proteins. [Lai MM, Cavanagh D (1997)]

The later reading frames encode the four major structural proteins: spike, envelope, membrane, and nucleocapsid.[Simmons et. al. (2013)] Interspersed between these reading frames are the reading frames for the accessory proteins. The number of accessory proteins and their function is unique depending on the specific coronavirus. [Lai MM, Cavanagh D (1997)]

Coronaviruses have the highest known frequency of recombination of any positive-strand RNA virus, promiscuously combining genetic information from different sources when a host is infected with multiple coronaviruses. In other words, these viruses mutate and change at a high rate, which can create havoc for both diagnostic detection as well as therapy (and vaccine) regimens.



PATHOPHYSIOLOGY

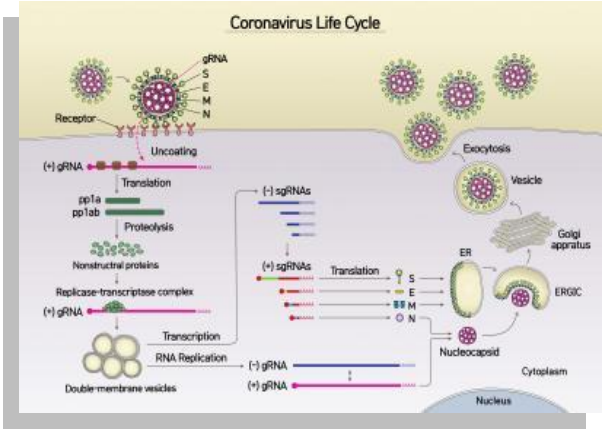
Attachment and entry

The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The sites of receptor binding domains (RBD) within the S1 region of a coronavirus S protein vary depending on the virus, with some having the RBD at the N-terminus of S1 (MHV), while others (SARS-CoV) have the RBD at the C-terminus of S1.[Kubo et. al. (1994)& Cheng et. al. (2004)] After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelop with the host membrane.[Simmons et. al. (2013)] S protein cleavage occurs at two sites within the S2 portion of the protein, with the first cleavage important for separating the RBD and fusion domains of the S protein [Belouzard et. al. (2009)] and the second for exposing the fusion peptide (cleavage at S2′). Fusion generally occurs within acidified endosomes, but some coronaviruses, such as MHV, can fuse at the plasma membrane. Cleavage at S2′ exposes a fusion peptide that inserts into the membrane, which is followed by joining of two heptad repeats in S2 forming an antiparallel six-helix bundle [Bosch et. al. (2003)] The formation of this bundle allows for the mixing of viral and cellular membranes, resulting in fusion and ultimately release of the viral genome into the cytoplasm.

Replication

The expression of the coronavirus replicase-transcriptase protein genes is mediated by the translation of the genomic RNA. The replicase-transcriptase proteins are encoded in open-reading frame 1a (ORF1a) and ORF1b and are synthesized initially as two large polyproteins, pp1a and pp1ab. The synthesis of pp1ab involves programmed ribosomal frame shifting during translation of ORF1a. During or after synthesis, these polyproteins are cleaved by virus-encoded proteinases with papain-like (PLpro) and chymotrypsin-like folds into 16 proteins; nsp1 to nsp11 are encoded in ORF1a, and nsp12 to nsp16 are encoded in ORF1b. The replicase-transcriptase proteins, together with other viral proteins and, possibly, cellular proteins, assemble into membrane-bound replication-transcription complexes (RTC). (We will use the term RTC to describe complexes copying or producing genome- or subgenome-length RNA.) These complexes accumulate at perinuclear regions and are associated with double-membrane vesicles. Hydrophobic transmembrane domains are present in nsp3, nsp4, and nsp6 and likely serve to anchor the nascent pp1a/pp1ab polyproteins to membranes during the first step of RTC formation.[Simmons et. al. (2013)]

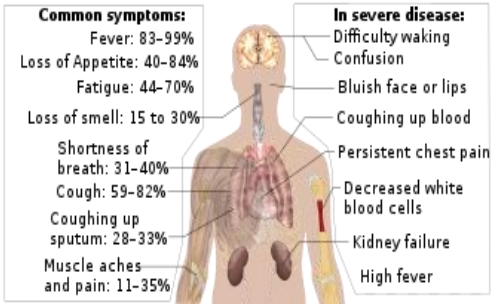
The mechanism of coronavirus replication hereby:



Release

The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number of accessory proteins.[Neuman et. al (2006)] RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. There, the M proteins direct most protein-protein interactions required for assembly of viruses following its binding to the nucleocapsid. [Sexton et. al. (2016)] Progeny viruses are then released from the host cell by exocytosis through secretory vesicles[Sexton et. al. (2016)].

SIGN AND SYMPTOMS



Using data from the plethora of novel coronavirus cases reported thus far, along with findings of the virus-related research studies, the Centers for Disease Control (CDC) and Prevention has added six new symptoms of COVID-19 to its list. Previously, the CDC had listed just three known symptoms of coronavirus infection: shortness of breath, cough, and fever. Now, six new additions have been made to this list, and they are as follows:

- Chills (the feeling of being cold without an apparent cause)
- Repeated shaking with chills
- Muscle pain
- Headache
- Sore throat
- New loss of taste or smell

The CDC states that these symptoms may appear 2-14 days after being exposed to the virus, and that people displaying these symptoms, or a combination of these symptoms, are likely to have contracted COVID-19. These symptoms may also range from mild to severe, it adds. [CDC (March 2020)]

EVALUATION

Most countries are utilizing some type of clinical and epidemiologic information to determine who should have testing performed. In the United States, criteria have been developed for persons under investigation (PUI) for COVID-19. According to the U.S. CDC, most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing). If a person is a PUI, it is recommended that practitioners immediately put in place infection control and prevention measures. Initially, they recommend testing for all other sources of respiratory infection. Additionally, they recommend using epidemiologic factors to assist in decision making. There are epidemiologic factors that assist in the decision on who to test. This includes anyone who has had close contact with a patient with laboratory-confirmed COVID-19 within 14 days of symptom onset or a history of travel from affected geographic areas (presently China, Italy, Iran, Japan, and South Korea) within 14 days of symptom onset.

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. The samples require storage at four degrees celsius. In the laboratory, amplification of the genetic material extracted from the saliva or mucus sample is through a reverse polymerase chain reaction (RT-PCR), which involves the synthesis of a double-stranded DNA molecule from an RNA mold. Once the genetic material is sufficient, the search is for those portions of the genetic code of the CoV that are conserved. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org, and subsequent confirmatory evaluation by additional labs. If the test result is positive, it is recommended that the test is repeated for verification. In patients with confirmed

COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance prior to being released from observation.

The availability of testing will vary based on which country a person lives in with increasing availability occurring nearly daily.

TREATMENT/MANAGEMENT

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

Most cases of COVID-19 are not severe enough to require mechanical ventilation or alternatives, but a percentage of cases are.[Murthy S et al; (March 2020)][WHO (28 January 2020)] The type of respiratory support for individuals with COVID-19 related respiratory failure is being actively studied for people in the hospital, with some evidence that intubation can be avoided with a high flow nasal cannula or bi-level positive airway pressure.[Wang K et al; (March 2020)]] Whether either of these two leads to the same benefit for people who are critically ill is not known.[Mc Enery et al;(April 2020)] Some doctors prefer staying with invasive mechanical ventilation when available because this technique limits the spread of aerosol particles compared to a high flow nasal cannula.[Murthy S et al; (March 2020)]

Severe cases are most common in older adults (those older than 60 years,[Murthy S et al; (March 2020)] and especially those older than 80 years).[Ferguson NM et al: (March 2020)] Many developed countries do not have enough hospital beds per capita, which limits a health system's capacity to handle a sudden spike in the number of COVID-19 cases severe enough to require hospitalisation.[Scott, Dylan (16 March 2020)] This limited capacity is a significant driver behind calls to flatten the curve.[Guan WJ et al ; (April 2020)] One study in China found 5% were admitted to intensive care units, 2.3% needed mechanical support of ventilation, and 1.4% died.[CDC (April 2020)] In China, approximately 30% of people in hospital with COVID-19 are eventually admitted to ICU.[CDC (April 2020)]

Intravenous (IV) treatment: This can treat and prevent dehydration and restore electrolytes to the body.

Sedative treatment: This can include antipsychotic or anti-anxiety medications. This treatment can help people who experience significant psychological distress, delirium, or confusion.

Other therapies

Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used. Preclinical studies suggested that remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections.[Hui et. al. (2019)] This drug was positively tested in a rhesus macaque model of MERS-CoV infection.[Gordon et. al. (2020)]

VACCINES IN TRIALS:

6 vaccines in human trials bring hope of early Covid-19 relief

If the trials are a success, scientists hope to have one million doses ready by September, and to dramatically scale up manufacturing after that.

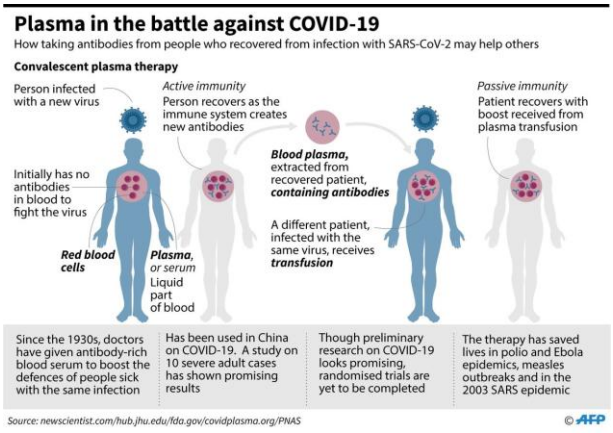
The availability of a safe and effective vaccine for COVID-19 is well-recognized as an additional tool to contribute to the control of the pandemic. At the same time, the challenges and efforts needed to rapidly develop, evaluate and produce this at scale are enormous. Phase one trials are small-scale, usually involving few participants, to assess whether the vaccine is safe for humans. Phase two trials often involve several hundred subjects, and mainly evaluate the efficacy of the vaccine against the disease. The final phase involves thousands of people to further assess the efficacy of the vaccine over a defined period of time, and can last several months

Nearly 70 ‘vaccine candidates’ are being tested and at least three have moved to the human clinical trial stage, but a vaccine for the novel coronavirus is unlikely to be ready for mass use before 2021. “While Zydus Cadila is working on two vaccines, Serum Institute, Biological E, Bharat Biotech, Indian Immunologicals, and Mynvax are developing one vaccine each," Gagandeep Kang, executive director of the Translational Health Science and Technology Institute, Faridabad, told PTI.

PLASMA THERAPY BECOMING A BOON FOR TREATING PATIENTS??

Convalescent plasma therapy is based on the concept of passive immunity, where antibodies of some disease developed in a person are used for treating others. Plasma in the blood contains antibodies, which helps to fight foreign pathogens. Once they have dealt with a certain kind of foreign element, some blood cells act as a memory cell and store information. When they come in contact with the same kind of pathogens again they

identify and defect it quickly by producing the same antibodies. The Covid19 is a new strain of virus so there is no artificial antibody available which can treat this disease. "The people who fought and recovered from coronavirus might have developed antibodies in their body, which can be a boon for others. Vaccination may take time to develop, but the need of the hour is to treat the patient, which can be possible by using these antibodies by plasma therapy." This is not the first time when plasma is being used for treating a medical condition. It was also used earlier during the Ebola outbreak. "Plasma can also be used in treating many conditions, especially when we need to treat autoimmune diseases where body produces antibodies against its cells and plasma helps to clear it via plasmapheresis."



REFERENCES

1 Cherry, James; Demmler-Harrison, Gail J.; Kaplan, Sheldon L.; Steinbach, William J.; Hotez, Peter J. (2017). Feigin and Cherry's Textbook of Pediatric Infectious Diseases. Elsevier Health Sciences. p. PT6615. ISBN 978-0-323-39281-5

2 "Chapter 24 - Coronaviridae". Fenner's Veterinary Virology (Fifth ed.). Academic Press. 2017. pp. 435–461. doi:10.1016/B978-0-12-800946-8.00024-6. ISBN 978-0-12-800946-8.

3 Woo PC, Huang Y, Lau SK, Yuen KY (August 2010). "Coronavirus genomics and bioinformatics analysis". Viruses. 2 (8):180420. doi:10.3390/v2081803. PMC 3185738. PMID 21994708. Coronaviruses possess the largest genomes [26.4 kb (ThCoV HKU12) to 31.7 kb (SW1)] among all known RNA viruses (Figure 1) [2,13,16].

4 Almeida JD, Berry DM, Cunningham CH, Hamre D, Hofstad MS, Mallucci L, McIntosh K, Tyrrell DA (November 1968). "Virology: Coronaviruses". Nature. 220(5168): 650. Bibcode:1968Natur.220..650.. doi:10.1038/220650b0

5 Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P, et al. (August 2006). "Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy". Journal of Virology. 80 (16): 7918–28. doi:10.1128/JVI.00645-06. PMC 1563832. PMID 16873249.

6 Fehr AR, Perlman S (2015). "Coronaviruses: an overview of their replication and pathogenesis". In Maier HJ, Bickerton E, Britton P (eds.). Coronaviruses. Methods in Molecular Biology. 1282. Springer. pp. 1–23. doi:10.1007/978-1-4939-2438-7_1. ISBN 978-1-4939-2438-7. PMC 4369385. PMID 25720466.

7 Lai MM, Cavanagh D (1997). "The molecular biology of coronaviruses". Advances in Virus Research. 48: 1–100. doi:10.1016/S00653527(08)602869. IN97801203984 85. PMC 7130985. PMID 9233431.

8 Cavanagh D, Mawditt K, Sharma M, Drury SE, Ainsworth HL, Britton P, Gough RE (August 2001). Schmidt A, Weber O, Wolff MH (eds.). "Detection of a coronavirus from turkey poults in Europe genetically related to infectious bronchitis virus of chickens". Avian Pathology. Birkhäuser Advances in Infectious Diseases BAID Birkhäuser. 30 (4): 355–68. doi:10.1007/3-7643-7339-3_1. ISBN 978-3-7643-7339-9. PMC 7123520.

9 Neuman, Benjamin W.; Kiss, Gabriella; Kunding, Andreas H.; Bhella, David; Baksh, M. Fazil; Connelly, Stephen; Droese, Ben; Klaus, Joseph P.; Makino, Shinji; Sawicki, Stanley G.; Siddell, Stuart G. (April 2011). "A structural analysis of M protein in coronavirus assembly and morphology". Journal of Structural Biology. 174 (1): 11–22. doi:10.1016/j.jsb.2010.11.021. ISSN 1047-8477. PMC 4486061. PMID 21130884.

10 Chang CK, Hou MH, Chang CF, Hsiao CD, Huang TH (March 2014). "The SARS coronavirus nucleocapsid protein—forms and functions". Antiviral Research. 103: 39–50. doi:10.1016/j.antiviral.2013.12.009. PMC 7113676. PMID 24418573.

11 Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. (April 2011). "A structural analysis of M protein in coronavirus assembly and morphology". Journal of Structural Biology. 174 (1): 11–22. doi:10.1016/j.jsb.2010.11.021. PMC 4486061. PMID 21130884.

12 Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, et al. (August 2003). "Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage". Journal of Molecular Biology. 331 (5): 991–

1004. doi:10.1016/S0022-2836(03)00865-9. PMC 7159028. PMID 12927536

13 Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S (December 2013). "Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research". Antiviral Research. 100 (3): 605–14. doi:10.1016/j.antiviral.2013.09.028. PMC 3889862. PMID 24121034.

14 Kubo H, Yamada YK, Taguchi F. Localization of neutralizing epitopes and the receptor-binding site within the amino-terminal 330 amino acids of the murine coronavirus spike protein. J Virol. 1994;68:5403–5410. [PMC free article] [PubMed] [Google Scholar]

15 Cheng PK, Wong DA, Tong LK, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet. 2004;363:1699–1700. [PMC free article] [PubMed] [Google Scholar]

16 Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S (December 2013). "Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research". Antiviral Research. 100 (3): 605–

17 Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A. 2009;106:5871–5876. [PMC free article] [PubMed] [Google Scholar]

18 Bosch BJ, van der Zee R, de Haan CA, et al. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77:8801–8811. [PMC free article] [PubMed] [Google Scholar]

19 Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S (December 2013). "Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research". Antiviral Research. 100 (3): 605

14. doi:10.1016/j.antiviral.2013.09.028. PMC 3889862. PMID 24121034.

20 Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P, et al. (August 2006). "Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy". Journal of Virology. 80 (16): 7918–28. doi:10.1128/JVI.00645-06. PMC 1563832. PMID 16873249.

21 Sexton NR, Smith EC, Blanc H, Vignuzzi M, Peersen OB, Denison MR (August 2016). "Homology-Based Identification of a Mutation in the Coronavirus RNA-Dependent RNA Polymerase That Confers Resistance to Multiple Mutagens". Journal of Virology. 90 (16): 7415–28. doi:10.1128/JVI.00080-16. PMC 4984655. PMID 27279608.

22 Chan JF, To KK, Tse H, Jin DY, Yuen KY. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol. 2013 Oct;21(10):544-55. [PMC free article] [PubMed]

23 Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, Gin T, Chan MTV. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur. Respir. J. 2019 Apr;53(4) [PubMed]

24 Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J. Biol. Chem. 2020 Apr 10;295(15):4773-4779. [PMC free article] [PubMed]

25 Murthy S, Gomersall CD, Fowler RA (March 2020). "Care for Critically Ill Patients With COVID-19". JAMA. **323** (15): 1499. doi:10.1001/jama.2020.3633. PMID 32159735. Archived from the original on 18 March 2020. Retrieved 18 March 2020.

26 World Health Organization (28 January 2020). "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected" (PDF). Archived (PDF) from the original on 26 February 2020. Retrieved 18 March 2020.

27 Wang K, Zhao W, Li J, Shu W, Duan J (March 2020). "The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China". Annals of Intensive Care. **10**(1): 37. doi:10.1186/s13613-020-00653-z. PMC 7104710. PMID 32232685.

28 McEnery T, Gough C, Costello RW (April 2020). "COVID-19: Respiratory support outside the intensive care unit". *The Lancet. Respiratory Medicine*. doi:10.1016/S2213-2600(20)301764. PMC 7146718. PMID 32278367.

29 Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M (16 March 2020). "Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand". Imperial College London. Table 1. doi:10.25561/77482. hdl:20.1000/100. Archived from the original on 21 March 2020. Retrieved 25 March 2020.

30 Scott, Dylan (16 March 2020). "Coronavirus is exposing all of the weaknesses in the US health system High health care costs and low medical capacity made the US uniquely vulnerable to the coronavirus". Vox. Archived from the original on 18 March 2020. Retrieved 18 March 2020.

31 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. (April 2020). "Clinical Characteristics of Coronavirus Disease 2019 in China". *The New England Journal of Medicine*. Massachusetts Medical Society. **382** (18): 1708-1720. doi:10.1056/nejmoa2002032. PMC 7092819. PMID 32109013.

32 Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)". *Centers for Disease Control and Prevention*. 6 April 2020. Archived from the original on 2 March 2020. Retrieved 19 April 2020.

AUTHOR'S INFORMATION

Ashwini .A. Mankar[1] (Assistant Professor)

mankarashwini3@gmail.com

Department of Biotechnology

Kamla Nehru Mahvidyalaya , Nagpur

CSIR NET , ARS NET, ICAR JRF AIEEA

Vijay.S. Harode[1] (Assistant Professor)

vijayharode29@gmail.com

Department of Biotechnology

Kamla Nehru Mahvidyalaya , Nagpur

CSIR NET , ARS NET, GATE, SET