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Review Article

Novel severe acute respiratory syndrome corona virus. A review of current status and strategies in India

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ABSTRACT

Corona viruses (RNA viruses) belongs to Coronaviridae family, comes under Nidoviridae family. It becomes important public health concern since the Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) outbreak in 2002 from Guangdong Province of Southern China. Continuous evolution of corona viruses was further highlighted with the emergence of Middle-East Respiratory Syndrome(MERS-CoV) outbreak in 2012 from Saudi-Arabia. Currently major concern is about the 2019 Novel CoV-2(SARS-CoV-2) that was initially identified in city of Wuhan, Hubei Province of China in December 2019. After the index case notified in China, First case of CoViD-19 was confirmed in January 2020 from India, and in March 2020 from Uttarakhand. In India there are about 800,000 active cases and about 150,000 deaths because of CoViD-19 by October 2020. Despite of that 70,00,000 cases recovered and get discharged from the CoViD centres. Uttarakhand contributed about 6000 active cases, 52000 recoveries and 1000 deaths by October 2020.Nonetheless, as the SARS-CoV and MERS-CoV were zoonotic infections but Recently, evidence of Inter-human only transmission of SARS-CoV-2 has been accumulated and thus, the outbreak seems to be spreading among humans throughout a large parts of Uttarakhand even in the hilly areas also. Here we are providing an update on features of CoViD-19, and Providing possible solutions how to halt expansion of this pandemic and also some updates on Convalescent Plasma.

1. Introduction

Coronaviruses are members of the subfamily Coronavirinae from the family Coronaviridae and the order Nidovirales. Based on Phylogenetic relationships and genomic structures, the subfamily Coronavirinae is divide into Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Deltacoronavirus. Alpha and beta only infect mammals. Gamma and delta infect birds and sometimes even infect mammals including rodents and bats. Gamma and Beta are causes respiratory illness in humans and stomach upset in animals.[1] Coronaviruses are enveloped and have single stranded positive sense RNA genomes that range in size from 26 to 32 kilobases because of that possibility of errors increases, which can result in rapid mutations. These mutations can give the virus new properties, such as the ability to infect new cell types or even new species that can generate serious lung disease.[2] A coronavirus particle consists of four structural proteins: the nucleocapsid, envelope, membrane and spike.[3] The Spike (S) protein forms club-shaped protrusions that stick out all over the virion, and looks like crown so the virus pronounced as Corona Virus. These protrusions interact with receptors on host cells thus determine the diversity of virus.

Animal CoVs causes important diseases in animals and is responsible for economic losses in domestic animals or birds.[4] These animal CoVs include avian infectious bronchitis virus (IBV), transmissible gastroenteritis virus

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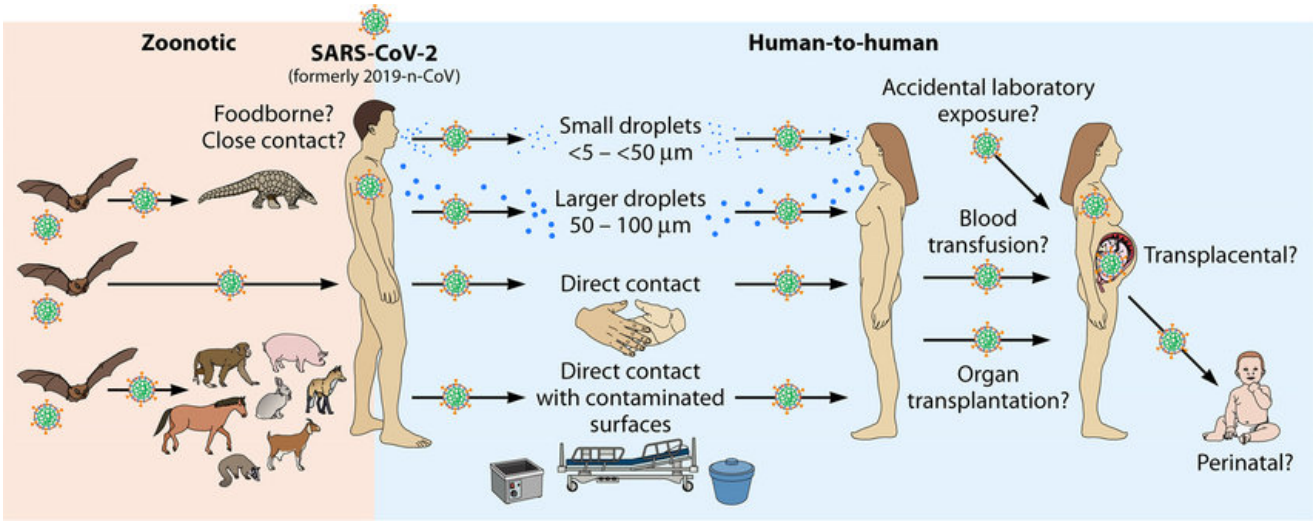

Fig. 1: Potential routes of Covid- 19 Disease spread

(TGEV), porcine epidemic diarrhea virus (PEDV), and more recently, swine acute diarrhea syndrome-CoV (SADS-CoV). Although rare, animal CoVs have the ability to infect humans and could further spread through human-to-human transmission.[5]

In the city of Wuhan, in Hubei Province, China, from December 2019, there were reports severe viral pneumonia. Sequencing from the patients revealed a novel CoV as the causative agent of this respiratory disease.[6] WHO named the Novel virus of 2019 as SARS-CoV-2 and ailment caused by it named as COVID-19. Prior to 2002, CoVs were treated never as serious viruses but things have been changed after serious illnesses caused by SARS-CoV and deaths caused in 2002-2003.[7] All three SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses are associated with serious respiratory diseases.[7] From the appearance, the SARS-CoV-2 has gained all attention from the world specially in India because of the dense population of the India. Efforts are underway in an attempt to control this new CoV outbreak.

In Uttarakhand, a hilly state where the Covid infection is brought up by the travelers coming from the different states of the India, took 2 months period after first case of Covid confirmed in India. And so the increase of Covid positive patients mainly from Roorkee, Haridwar, Udham Singh Nagar, Rudrapur, Dehradun district of the Uttarakhand which are mainly non hilly. After about 1 month the hilly areas are also get involved with the Covid infection. As in the hilly areas the oxygen pressure is also low as compared to the non hilly areas the severity of disease is more in hilly areas. So we try to give some promising advices for the people residing in the hilly areas for the prevention of severe disease along with the safety measures of social distancing, Proper hand washing and personal protection equipments like mask, gloves etc.

2. Pathogenesis

There are three phases of corona virus infection.

2.1. Phase 1

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV2 and SARS-CoV.[8] In vitro data with SARS-CoV indicate that the ciliated cells are primary cells infected in the conducting airways.[9] The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. Perhaps super spreaders could be detected by these studies. For the RT-PCR cycle number to be useful, the sample collection procedure would have to be standardised. Nasal swabs might be more sensitive than throat swabs.

2.2. Phase 2

The virus propagates and migrates down the airways (respiratory tract), and an innate immune response is triggered roburstly. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. At this time, the disease COVID-19 is clinically manifest. The level of CXCL10 (early response cytokine) may be predictive of clinical outcome.[10] Viral infected epithelial cells are a major source of beta and lambda interferons.[11] CXCL10 is an interferon responsive gene gives signal in the alveolar type II cell which respond to both SARS-CoV and influenza.[12] CXCL10 has also been reported to be useful as disease marker in SARS.[13] Determining the host innate immune response might improve predictions on the subsequent course of the disease and need for more aggressive monitoring. For about 80% of the infected patients, the disease will be

mild and mostly restricted to the upper and conducting airways. These individuals may be monitored at home with conservative symptomatic therapy.

2.3. Phase 3

Unfortunately, about 15% to 25% of the infected patients gets stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age.

The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells.[14] SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. Thereafter a self-replicating pulmonary toxin released as viral particles which infects type II cells in adjacent units. Lung will likely to lose most of their type II cells, and secondary pathway for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells.[15]

This postulated sequence of events has been shown in the Murine model of influenza pneumonia.[16] The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells.[17] The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of ARDS. There are significant knowledge gaps in the pathogenesis of COVID-19 that will be filled in over the next few months to years. On the assumption that viral entry by SARS-CoV-2 will be the same as SARS-CoV. We do not know if there are alternate receptors for viral entry. CD209L is an alternative receptor for SARS-CoV.[18]

We await detailed studies on infection and the innate immune response of differentiated primary human lung cells. The apical cilia on airway cells and microvilli on type II cells may be important for facilitating viral entry. Different phases of Covid Infection alarming for testing and get medical advice.

3. Clinical Features of the Covid-19

CDC provided with the symptomatology of the Covid-19. Which are alarming and diverse with every new clinical presentation.

The clinical sign and symptoms of Covid infection are very common flu like initially. It starts with simple with mild headache, body ache, malaise, anorexia, loss of taste sensations, fever or chills (fever can be of low grade with or without chills), rarely presents as vomiting and diarrhea, loss of smell sensation also noted. Symptoms can range from mild to severe illness, and appear 2-14 days after you are exposure of COVID-19.

Usually health recovered without you gets the severity of infection. unfortunately if disease severity increases then features like trouble breathing, persistent pain or pressure in the chest, confusion, inability to wake or stay awake, bluish lip or face also occurred; on any of above symptom one should urgently seek medical care.

4. Specimen Collection, Packaging and Transport Guidelines for 2019 Novel Coronavirus (2019-NCOV)

4.1. Selection of patient

Presentation of Severe Acute Respiratory Illness (SARI), and one of the following i.e. a travel history from contaminated area prior to onset of symptoms; healthcare workers working, unusual or unexpected contact history to Covid confirmed person, especially sudden deterioration despite appropriate treatment; should be urgently investigated. Case definition is updated as per MOHFW, GOI.

4.2. Specimen collection details

(Adapted from the WHO guidelines on 2019-nCoV)(Table 1).

5. Specimen Labeling and Processing

1. The person should use the Personal protective equipment's (apron, hand gloves, face shield, N95 Masks etc.) and follow all biosafety precautions so as to protect individuals and the environment.
2. Proper labeling (name/age/gender/specimen ID) need to be done on specimen container and other details of sender (name/address/phone number) on the outer container by mentioning "To be tested for 2019-nCoV".

6. Diagnosis of SARS-CoV-2 (COVID-19)

Real-time RT-PCR or next-generation sequencing techniques are used to confirm the diagnosis of SARS-CoV-2 (COVID-19) cases.[19] In confirming the diagnosis in clinical cases of COVID-19 nucleic acid detection techniques, like RT-PCR, are considered an effective method.[20] Across the globe Several companies focuses on developing and marketing SARS-CoV-2-specific nucleic acid detection kits. Multiple laboratories are also developing their own in-house RT-PCR.

Recently, 95 full-length genomic sequences of SARAS-CoV-2 strains available in the National Center for Biotechnology Information and GISAID databases were subjected to multiple-sequence alignment and Phylogenetic analyses for studying variations in the viral genome. The molecular biology and pathobiology studies on SARS-CoV-2 could pave the way for developing diagnostic, preventive

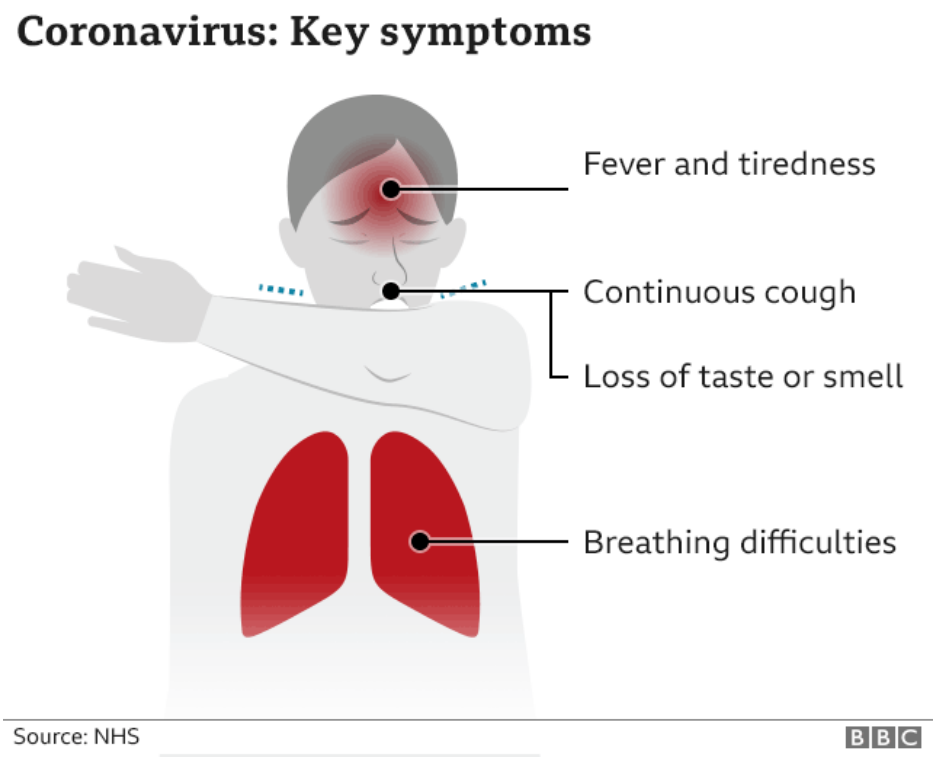

Fig. 2: Different phases of Covid Infection alarming for testing and get medical advice

Table 1: Samples used for the COViD detection

Specimen	Collection material	Storage temperature	Comments
# Nasopharyngeal swab and Oropharengeal swab	Dacron or *Polyester flocked swabs	-70 degree Celsius	Swabs should be placed in the same tube to increase the viral load.
# Serum (2 samples acute and convalescent)	Serum separator tubes (3-5 ml whole blood)	-70 degree Celsius	Collect paired samples: Acute – first week of illness Convalescent – 2 to 3 weeks later
# Whole blood (5ml)	EDTA vial	-70 degree Celsius 4 degree Celsius only if used within 4 days.	Not applicable
Bronchoalveolar Lavage	*sterile container	-70 degree Celsius	Dilution of pathogen take place.
Nasal wash, Air way aspirates	*sterile container	-70 degree Celsius	Not applicable
Biopsy/ Autopsy	sterile container with saline	-70 degree Celsius	Usually avoided autopsy samples
Sputum	*sterile container	-70 degree Celsius	Ensure the material is from the lower respiratory tract

*For transport of samples for viral detection, use VTM (viral transport medium) containing antifungal and antibiotic supplements. Repeated freezing and thawing of samples is avoided.
*All specimens should be transported at 4 degree Celsius.
Priority specimens- Other specimens need to be sent as per the clinical condition of the patient

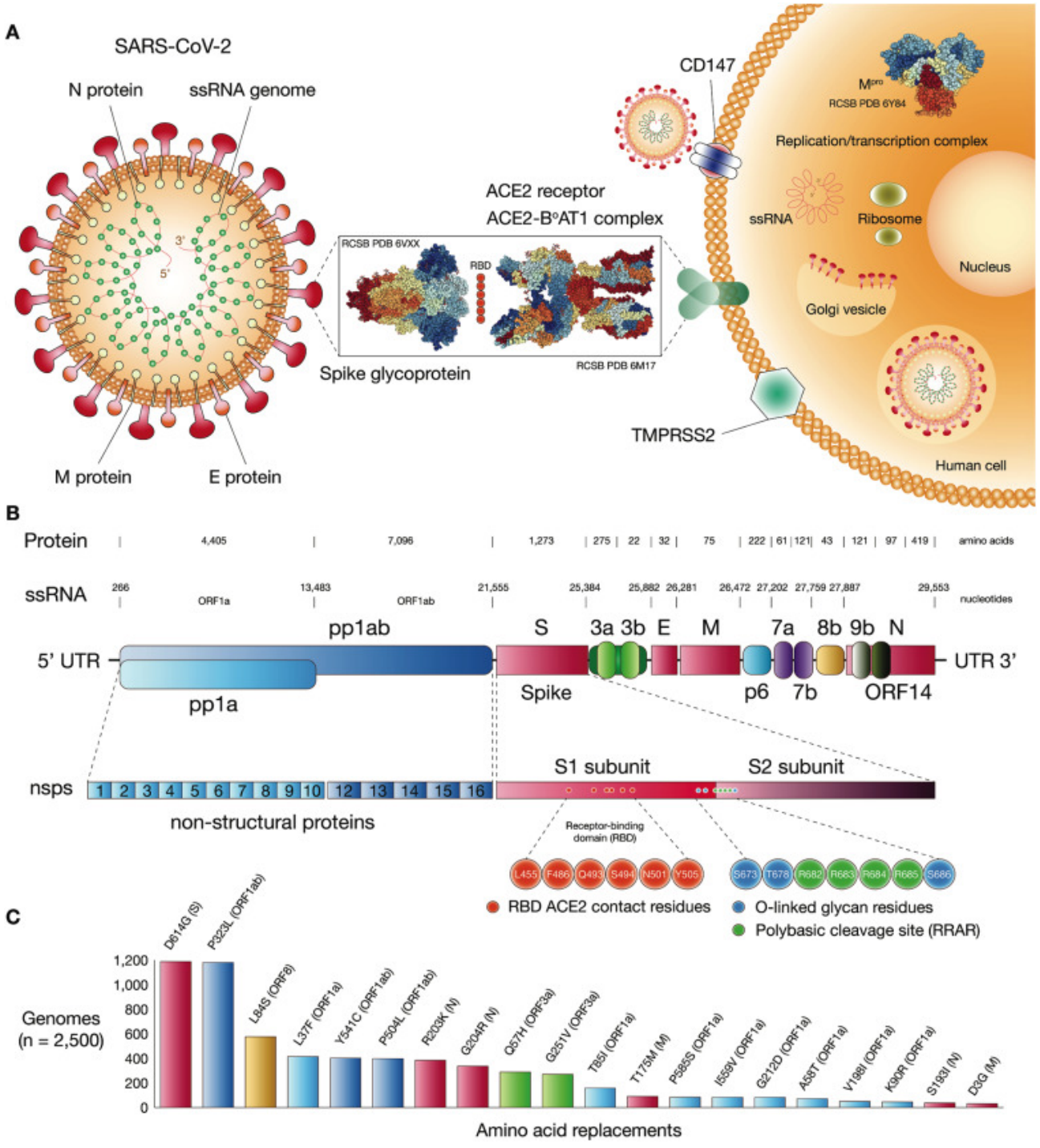

Fig. 3: Overall structure and pathogenesis of SARS-CoV-2.

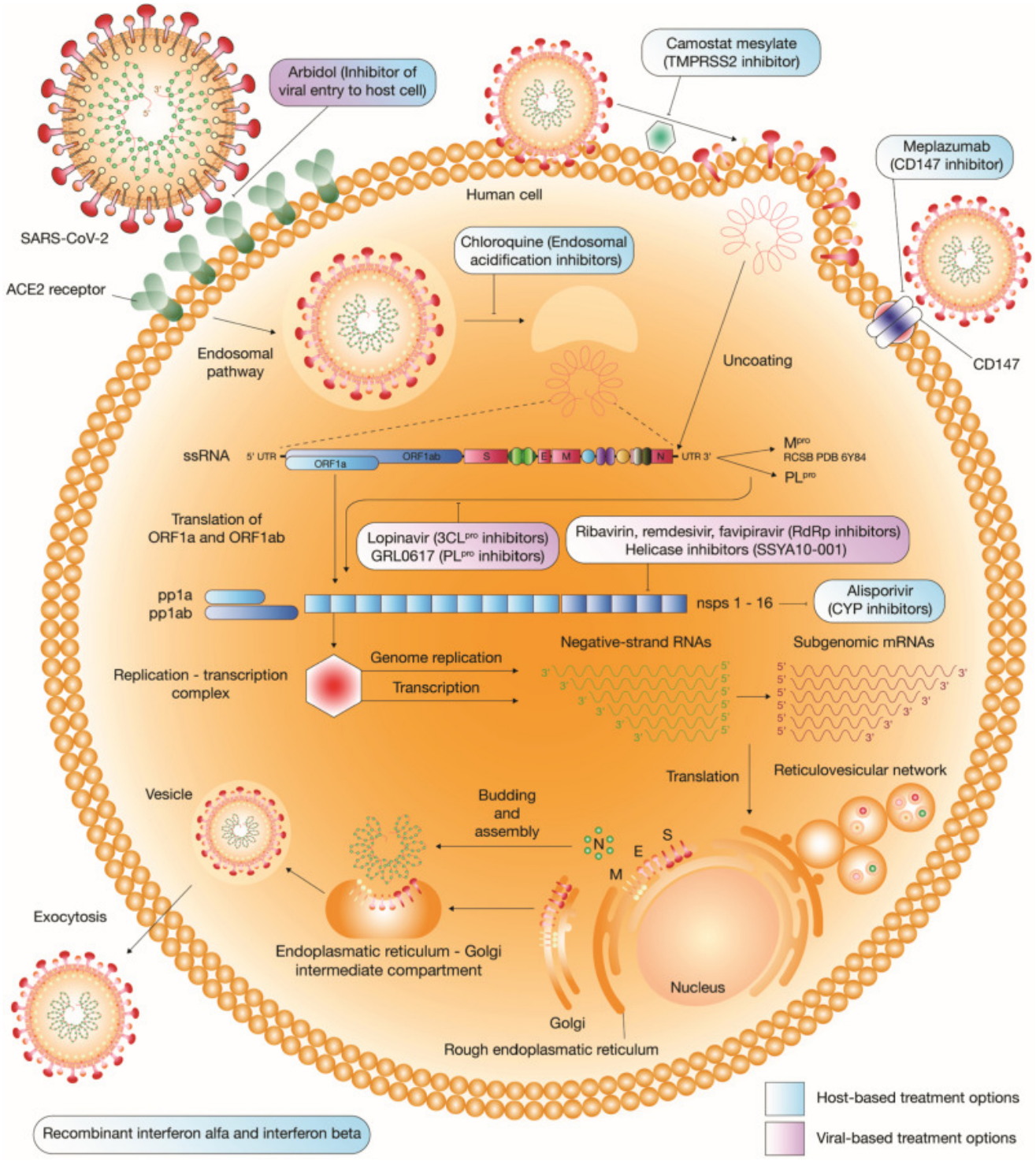

Fig. 4: SARS-CoV-2 Replication cycle and its inhibitors. SARS-CoV-2 infection strikes through spike (S) protein to the host cell receptor. One out of two: angiotensin-converting enzyme 2 (ACE2) and CD147. After the strike, S protein dismantled by the cell surface-associated transmembrane protease serine 2 TMPRSS2 promotes the fusion of viral and cell membranes. Followed by release of the nucleocapsid into cytoplasm, then genomic RNA gets translated via ribosomal frameshifting to produce polyproteins pp1a and pp1ab, which undergo cotranslational proteolytic processing into the 15 non-structural proteins (nsp1- nsp10 and nsp12-nsp16) that form the replication-transcription complex (RTC). RTC is involved in the genomic RNA replication and in the transcription of a set of nested subgenomics mRNAs required to express the structural and accessory protein genes. New virions starts budding into the intracellular membranes of ER-Golgi intermediate compartment and released through exocytosis. Additionally, there are detailed host-based treatment options (blue) and viral-based (pink).
(Source: Ortiz-Prado et al / Diagnostic Microbiology and Infectious Disease 98 (2020 115094)

and control strategies.[21] N-gene-specific quantitative RT-PCR is used to measure the viral loads of SARS-CoV-2 in throat swab and sputum samples collected from COVID-19-infected individuals. The viral load shoots at around 5 to 6 days following the onset of symptoms, and it ranged from 104 to 107 copies/ml during this time.[22] In another study, the viral load was found to be higher in the nasal swabs than the throat swabs obtained from COVID-19 symptomatic patients.[23] It was believed that higher the viral load poorer the outcome, but some case reports have shown asymptomatic individuals with high viral loads also.[24] In South Korea, study revealed that the Kinetics of the virus is significantly different from earlier reported CoV infections, including SARS-CoV.[25] Studies are needed to establish correlation between SARS-CoV-2 viral load and cultivable virus. Recognizing patients with fewer or no symptoms, along with having modest detectable viral RNA in the oropharynx for 5 days, indicates the requirement of data for assessing SARS-CoV-2 transmission dynamics and updating the screening procedures in the clinics.[26]

The virus harbor the upper respiratory tract for the proliferation and used to shed away after the remission of the symptoms to the individuals, including via stool. Which demands current case definition updating with reassessment of adoptive strategies for restraining the SARSCoV-2 outbreak.[27] In a recent survey stool samples were found to be positive on RT-PCR analysis after the 13 days of remission of symptoms of the disease. Although the stool sample contain less viral load than those of respiratory samples (range, 550 copies per ml to 1.21 105 copies per ml), this has essential biosafety implications.[28] In Singapore study containing 18 SARS-CoV-2-positive patients, traveled from Wuhan showed the RT-PCR confirmed viral RNA in stool and whole blood.[29] There is also fecal excretion documented for SARS-CoV and MERS-CoV, along with the capability of fecal-oral transmission. Thus, SARS-CoV-2 has every potential for fecal-oral transmission. Areas of low standards of hygiene and poor sanitation have a greater risk for Fecal-oral transmission of SARS-CoV-2, may have risk for high spread of this virus. The corona virus is affected via Ethanol and disinfectants containing chlorine or bleach.[30] More than half of the India is having dense packed population and which increases the risk of transmission so many folds in India which has been pictured form march to October 2020 and yet to come.

More recently, other advanced diagnostics have been designed and developed for the detection of SARS-CoV-2.[31] A reverse transcriptional loop mediated isothermal amplification (RT-LAMP), namely, iLACO, has been developed for rapid and colorimetric detection of this virus.[32] RT-LAMP serves as a simple, rapid, and sensitive diagnostic method that does not require sophisticated equipment or skilled personnel.[33]

7. Vaccines, Therapeutics, and Medicines

We need to depend solely on implementing effective infection control measures because of lack of effective antiviral therapy and vaccines in the present scenario to decrease transmission. Recently, the receptor for SARS-CoV-2 was established as the human angiotensin-converting enzyme 2 (hACE2), and the virus was found to enter the host cell mainly through endocytosis. There is a critical role of PIKfyve, TPC2, and cathepsin L in viral entry to host cell. These findings are critical, since the components described above might act as candidates for vaccines or therapeutic drugs against SARS-CoV-2.[34]

7.1. Vaccines

In the induction of protective immunity S protein plays a role for SARS-CoV by mediating T-cell responses and neutralizing antibody production. Earlier, several attempts to develop a vaccine against human Coronaviruses by using S protein as the target have been tried.[35] However, due to a lack of cross-protection minimal application of the developed vaccines noted. Of note, the result was conclusive that the expression of M, E, or N proteins without the presence of S protein would not confer any noticeable protection, with the absence of detectable serum SARS-CoV-neutralizing antibodies.[36] Therefore, vaccine strategies based on the whole S protein, S protein subunits, or specific potential epitopes of S protein appear to be the most promising vaccine candidates against Coronaviruses. The comparative analysis confirmed that S1 subunit of S protein, is an important vaccine target.[37]

The collaborative effort of the researchers of Rocky Mountain Laboratories and Oxford University is designing a chimpanzee adenovirus-vectored vaccine to counter COVID-19.[38] The Coalition for Epidemic Preparedness Innovations (CEPI) has initiated three programs to design SARS-CoV-2 vaccines.[39]

1. CEPI has a project for designing a MERS-CoV DNA vaccine that could be effective.
2. A molecular clamp vaccine is under designing by CEPI and the University of Queensland for MERS-CoV and other pathogens, which could easily identify the pathogen.
3. Moderna has been funded from CEPI to develop a vaccine for COVID-19 in partnership with the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH).[40]

Jennifer Haller gets first experimental vaccine on 16 March 2020 outside of China, developed by Moderna, against this pandemic virus. Along with China's CanSino Biologics, Moderna became the first research group to launch small clinical trials of vaccines against COVID-19. Their study is

evaluating the vaccine's safety and ability to trigger immune responses.[41]

There is a need for the development of a pan-coronavirus vaccine that can produce cross-reactive antibodies because of recurring nature of virus. However, the success of such novel vaccine relies greatly on its capability to produce protection for the present versions of the virus and also to the viruses which could possibly emerge in the future. Most vulnerable group for the viral infection is the pregnant women. Due to alterations in the immune system and physiological systems that are associated with pregnancy. Therefore, in the event of successful vaccine development, pregnant women will not get access to the vaccines.[42] so, there is need for recommendation for the pregnant women to be included in the ongoing vaccine trials, since successful vaccination in pregnancy will save more lives.

7.2. Therapeutics and drugs

Effective drugs for management of COVID-19 infections are remdesivir, lopinavir/ritonavir or in blend with interferon beta, convalescent plasma, and monoclonal antibodies (MAbs). However, there are efficacy and safety issues with these drugs so these drugs require additional clinical trials.[43] A controlled trial of ritonavir boosted lopinavir and interferon alpha 2b treatment was performed on COVID-19 hospitalized patients (ChiCTR2000029308).[44] Still, no full-proof clinical trials have been published for the use of hydroxychloroquine and tocilizumab for their potential role in modulating inflammatory responses in the lungs and antiviral effect.[45] Recently, no benefit from lopinavir-ritonavir treatment over standard care also reported in a clinical trial conducted on adult patients.[46]

Plasma therapy is a new strategy for look the treating opportunities in COViD patients but this is not a magic bullet. As every patient is not responding for this therapy.

I suppose that there are few mistakes in processing of plasma therapy which usually not taken care by the clinicians:

1. Plasma must contain antibodies which are against S1-RDB or spike antigen.
2. The antibodies used should be of IgG type.
3. Plasma should have enough antibodies.
4. Use of plasma in early phase/ moderate disease. The idea behind the plasma is to neutralize the virus, so one should try to kill early. What is use of plasma in ICU patient, critically ill who is already suffered the severe organs damage which are mostly irreversible. Plasma is not a magic bullet..
5. Also I am suggesting to make the viral road of patient as the standard indications for use of convalescent plasma so clinicians can prevent more ICU admissions and prevent the severe organ damage which might prevent the mortality.

Chloroquine is an antimalarial drug known to possess antiviral activity due to its ability to block virus-cell fusion by raising the endosomal pH necessary for fusion. It also interferes with virus-receptor binding by interfering with the terminal glycosylation of SARS-CoV cellular receptors, such as ACE2.[47]

8. Prevention, Control, and Management

1. Personal protective equipment (PPE), like face masks, will help to prevent the spread of respiratory infections like COVID-19. While traveling via public transport systems face masks protect from infectious aerosols as well as prevent the transmission of disease.[48] The main key for avoiding the risk of infection is Social distancing
2. The maintenance of hand hygiene is another practical aspect to reduce the transmission of respiratory diseases. Both hand hygiene and face masks help in reduces the risk of COVID-19 transmission.[49]
3. The hospital staff must be trained and knows every method of prevention and protection so that they become competent enough to protect themselves and others.[50]
4. The wet market plays the role of intermediate host of SARS-CoV-2, there is a need for strengthening the trading regulatory mechanism globally.[51]
5. Closed environment provides an ideal space for the outburst of respiratory disease outbreaks.for eg; airplanes and cruise ships. So avoid travelling in cruises and airplanes because they might carry pathogen to many countries.
6. Large-scale testing, contract tracing, and localized quarantine of suspected cases for limiting the spread of this pandemic virus is key to break the spread of the viral disease.
7. However, the real issue is how we are planning to counter the next zoonotic CoV epidemic that is likely to occur within the next 5 to 10 years or even sooner. As the past is suggesting the near coming CoV again in between 2027 to 2030. SARS in 2002 after 7 years MERS in 2012 followed by COVID-19 in 2019 and further evolving virus is yet to come.

9. Conclusion

After SARS epidemic globally over several years, the current pandemic reminds of how novel pathogens can rapidly emerge and propagate, and can lead to the severe public health issue. A long journey of researches need to be conducted for establishment of animal models for SARS-CoV-2. Which could further used to investigate the replication, transmission dynamics, and pathogenesis in humans as well. Present trends suggesting that the

climate change and ecological conditions are associated with human-animal contact. Live-animal markets, such as the Huanan South China Seafood Market, represent ideal conditions for interspecies contact of wildlife with domestic birds, pigs, and mammals. Fever, cough, expectoration, headache, and myalgia or fatigue are the most suggesting symptomatology of the COVID-19. Asymptomatic and atypical clinical manifestations were also identified, which complexes the disease transmission dynamics. Atypical clinical manifestations, clinician must be very attentive to prevent misdiagnosis.

The real question is, how are we planning to counter the next zoonotic CoV epidemic that is likely to occur within the next 5 to 10 years or perhaps sooner? Our knowledge of most of the bat CoVs is scarce, as these viruses have not been isolated and studied, and extensive studies on such viruses are typically only conducted when they are associated with specific disease outbreaks. The next step following the control of the COVID-19 outbreak in India should be focused on screening, identification, isolation, and characterization of CoVs present in wildlife species of India. Both in vitro and in vivo studies (using suitable animal models) should be conducted to evaluate the risk of future epidemics. Presently, licensed antiviral drugs or vaccines against SARSCoV, MERS-CoV, and SARS-CoV-2 are lacking. However, advances in designing antiviral drugs and vaccines against several other emerging diseases will help develop suitable therapeutic agents against COVID-19 in a short time. Until then, we must rely exclusively on various control and prevention measures to prevent this new disease spread.

10. Source of Funding

None.

11. Conflict of Interest

The authors declare that there is no conflict of interest.

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