

Novel Coronavirus Disease (COVID-19): A Comprehensive Review.

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Abstract

The Corona Virus Disease 2019 is an emerging public health emergency throughout the world. According to World Health Organization, COVID-19 outbreak appeared as Severe Acute Respiratory Illness later culminating to pneumonia of unknown etiology. The burden of cases is highest in Italy (985.63 cases per million) and lowest in India (0.3 cases per million). Coronaviruses are enveloped, single stranded positive sense RNA viruses, which belong to the subfamily Coronavirinae of Coronaviridae family and have around 70 – 80% of sequence homology with the already known SARS-CoV. It is a zoonotic disease with no established intermediate host. In humans, the disease spreads via respiratory droplets. This disease doesn't have any established treatment protocol or vaccine despite earlier outbreaks of different Coronaviruses.

Keywords: Coronavirus disease-19, SARS-CoV-2, Middle East Respiratory Syndrome, Real Time-Polymerase Chain Reaction

Introduction

The Corona Virus Disease 2019 (COVID-19) is an emerging public health emergency throughout the world including Western Pacific, European, South-East Asia,

Eastern Mediterranean Regions, regions of the Americas and Africa. It appears to have started in Wuhan city of China as a cluster of pneumonia of unknown etiology and initially temporarily named as 2019-novel Corona Virus by World Health Organization on January 7, 2020 [1]. The International Committee on Taxonomy of viruses (ICTV) recognized this virus on the basis of phylogeny and taxonomy as a sister to SARS-CoV of the species SARS related coronavirus and renamed “SARS-CoV-2” since it shares around 70 – 80% of sequence homology with the already known SARS-CoV [2]” According to WHO, COVID-19 outbreak appeared as Severe Acute Respiratory Illness (SARI) later culminating to pneumonia of unknown etiology. Initially the disease appeared in 44 cases only, but steeply rose to 462684 confirmed cases and 20834 deaths globally (195 countries) in very short span of 85 days [3,4]. The most affected countries represent China, Italy, USA, Spain, Germany, Iran, France and India. The burden of cases is highest in Italy (985.63 cases per million) and lowest in India (0.3 cases per million). Local transmission is being reported from more than 114 countries across the world and rapidly spreading in the areas which are densely populated, and resources

limited such as India and Pakistan and several more third world countries.

Despite several outbreaks of coronaviruses in humans in different forms, from SARS to MERS to latest CoVID-19, there is a huge gap in research on, specific vaccine and treatment.

The objective of this study is to review the current challenges of COVID-19, clinical characteristics and therapeutics including role of ancient medicine, measures for containment to get rid of ongoing threat of wiping whole civilization.

Coronaviruses and their diversity: Coronaviruses (CoVs) are enveloped, single stranded positive sense RNA viruses, which belong to the subfamily Coronavirinae of Coronaviridae family. The family is further subdivided into four genera, α -CoVs, β -CoVs, γ -CoVs, and δ -CoVs, and only first are known to cause diseases in humans and last two tend to infect birds and occasionally mammals [5,6]. Many new coronaviruses have recently been discovered and categorized genetically [7]. The CoVs genome, ranging from approximately 25 to 32 kilobases (kb) in size, and is probably the largest of all RNA viruses known, size 120 – 160 nm. As already known, there are seven CoVs known to cause human diseases including Human coronavirus 229E, NL63, OC43, HKU1, SARS-CoV (Severe Acute Respiratory Syndrome) coronavirus and MERS-CoV (Middle East Respiratory Syndrome) coronavirus and the latest SARS-CoV2 [1]. The low pathogenic CoVs, including 229E, HKU1, OC43 and NL63, account for 10% to 30% of upper respiratory tract infections and typically cause mild respiratory diseases [8]. In contrast, the highly pathogenic SARS-CoV and MERS-CoV, predominantly infect lower air- ways and cause fatal pneumonia. SARS-CoV2, a novel CoV was identified in December 2019 in the Chinese city of Wuhan by next generation sequencing. It belongs to the lineage of

β -CoVs, subgenus sarbecovirus [9,10]. The genome is arranged in order of 5' UTR-replicase (orf1a/b)-Spike(S)-Envelope(E)-Membrane(M)-Nucleocapsid(N)-3'UTR. S, E, M, N encodes structural proteins [9]. It can replicate in human airway epithelial cells to cause relatively milder clinical symptoms than SARS and MERS [11].

Epidemiology: Epidemiologically, COVID-19 is a zoonotic disease and spread of infection in human has been zeroed down to exposure to a seafood market in Wuhan city of China. The primary mode of spread of the epidemic is person-to-person transmission. It has been speculated in one study, that bamboo rats, raccoons, and snakes might had be the original source of infection from where it originally originated. [12] As of now, there is no confirmatory research which can pinpoint the intermediate host. The pangolins have been suspected to be the connecting bridge, but it may not be the only one and also no authentic study to support this speculation. [13] The route of infection appears to be direct or indirect contact of the mucosae with infectious respiratory droplets from cough or sneezes and fomites. The presence of viral nucleic acids in stool creates suspicion of possibility of feco-oral transmission, but still unconfirmed due to lack of conclusive studies. A 30-hour old newborn was confirmed with 2019-nCoV in Wuhan Children's Hospital suggests vertical transmission also but there are no conclusive studies to claim it. However, human conjunctival epithelium has been claimed to be contaminated with infectious droplets [14]. The virus on smooth surfaces retain its viability for over 5 days at temp 22–25 °C and relative humidity of 40-50%, whereas at higher temperature and higher relative humidity (temp 38 °C and relative humidity of >95%) viral viability get rapidly lost and becomes inactivated [15]. The incubation period after infection is generally 2 to 14 days [16]. 2019-nCoV is highly infectious with about 2 h survival time in

the air and all age groups are susceptible to the virus, while elderly patients with comorbid conditions are at more risk to experience severe illness as evident by present global scenario.[17] Asymptomatic as well as symptomatic patients (but more of symptomatic cases) can transmit infection as compared to cases before onset of clinical illness. The speed of disease transmission depends on basic reproduction rate (R_0), the rate reflecting speed of disease transmission. The recent study published by Chinese Center of Disease Control estimated R_0 as 2.68. This finding is also supported by rate published by WHO. This clearly explains that infection rate is directly proportional to R_0 . R_0 of value 1 is the reference value, beyond which it becomes a public health emergency. Citing this WHO on January 30, 2020 declared nCoV-2019 a public health emergency of international concern and since then it had adopted all measures to bring the R_0 to below 1 globally [18-20]. The spread of infection of COVID-19 outbreak is occurring more rapidly than it was observed in MERS and SARS epidemics, probably due to lower Case Fatality Ratio (CFR) of about 2-5% as compared to 35% in MERS and 11% in SARS, but the CFR in COVID-19 still needs to be interpreted with caution since the pandemic still ongoing.[21]

Clinical Characteristics and diagnosis: All age groups are susceptible to COVID-19 infection, while elderly patients with comorbid conditions are more likely to experience severe illness. The disease shares many similarities with SARS. The most common symptoms are fever (87.9%) notably the first manifestation, fatigue (69.6%), dry cough (67.7%), myalgia (34.8%), shortness of breath and these may often be accompanied with, rhinorrhoea, sore throat and diarrhea in few patients. Serious cases can lead to pneumonia, severe acute respiratory syndrome, kidney failure and death. A part of the patients may experience, dyspnea, hypoxemia leading

to Acute Respiratory Distress Syndrome (ARDS), septic shock, metabolic acidosis and even Multi Organ Dysfunction (MODS) in very few cases. Routine laboratory findings like lymphopenia, leucopenia and thrombocytopenia may indicate early illness, but most of the cases show elevated C-reactive protein levels [22]. All these laboratory findings just provide corroborative evidences to the clinical findings. According to recent studies conducted in China, reveal that most of the confirmed cases suffered from pneumonia with ground glass opacity and bilateral patchy shadowing in the chest CT. Most of the patients have good prognosis except elderly with comorbidities like diabetes, hypertension and ICU patients where mortality may reach up to 17-38% [23,24]

Epidemiological risks, clinical features and laboratory tests are key to establish diagnosis. The illness has seen many case definitions right from beginning with fever and travel to Wuhan China, contact with a confirmed case to the present definition where all symptomatic cases of Severe Acute Respiratory Illness (SARI) have to be investigated in detail.

Real Time Polymerase Chain Reaction (RT-PCR) is the mainstay of diagnosis as of now when this article is being written. As of now two types of RT PCR protocols are being followed by different labs in India as per the guidelines of Indian Council of Medical Research (ICMR) and National Institute of Virology Pune published (Document no: SP.01 and SP.02, Issue No.: 01). First is, the screening assay and other being the confirmatory assay. The screening assay detects only E gene while the confirmatory assay detects besides E gene, N gene, RdRp gene and ORF 1b gene also.

The RT PCR, although very sensitive and specific, requires, advanced infrastructure and expertise. For a resource limited country like India, where majority of

population is rural and has limited access to healthcare, a robust point of care test is much needed. Hence research needs to be focused to modify to bring the molecular diagnosis at peripheral level

Treatment available: Although many treatment modalities have been explored and still being experimented but till date there is no specific therapy to combat the virus. Since the etiological agent is an RNA virus and it has been claimed through unclaimed reports that the replication strategy and assembly of virion mimics that of Human Immunodeficiency Virus (HIV), hence protease inhibitors like lopinavir and ritonavir have been tried on patients [25,26]. Nelfinavir and Remdesivir are claimed to be potential novel nucleotide analogue and have been claimed to be pan coronaviral antiviral drugs [27-29]. Chloroquine and Arbidol, (a broad-spectrum antiviral drug), have also been tried with doubtful success but a study from China claims it to have potential antiviral effect of nCoV19 while arbidol is under phase 4 clinical trial in china [30]. Several researches have shown promising results of combining drugs with monoclonal antibodies (mAB) which is claimed to bind receptor binding domain, thus it may be a potential therapeutic option to treat cases of nCoV19 infection [31]. Baricitinib, a janus kinase inhibitor disrupts the receptor mediated endocytosis, thus inhibiting viral entry into the cells of lung and can be potential treatment choice in future [32].

Herbal medicines and purified natural products provide rich source of antiviral agents. It is claimed that these products interact with viral life cycle at different points thus paving a way to plethora of many promising antiviral drugs. As of now there are no specific herbs which can cure the COVID 19 but as claimed in one study, saikosaponins which are naturally occurring triterpene glycosides from the plants *Bupleurum*, *Heteromorpha*

and *Scrophularia scorodonia*, also known as balm leaved figwort, have shown antiviral effects on HCoV-22E9. These agents effectively prevent early stages of HCoV-22E9 infection. But the most promising results have been shown by extracts of *Lycoris radiata* commonly known as sunrise lily, hell flower, red magic lily, equinox flower and hurricane, commonly grown as ornamental plant. *Artemisia annua*, mostly grown in Manipur, also known as sweet wormwood, sweet annie, sweet sagewort, annual mugwort or annual mugwort; agnidamini, bahukantaka, damanka (Sanskrit), majtari (Hindi) and Arthmasia Baranjasi (Urdu), have shown potential antiviral effects on SARS-CoV. *Pyrrosia lingua*, felt fern or tongue fern, grown as ornamental plant in China and Japan, including *Lindera neesiana*, all these Chinese medicinal herbs have been claimed to possess anti SARS CoV effects. Myricetin, scutellarin, and phenolic compounds of *Isatis indigotica* and *Torreya nucifera*, also known as Japanese nutmeg and is big tree forestation of North Eastern UP, have been identified as potential inhibitors of SARS CoV enzymes nsp13helicase and 3CL protease. *Houttuynia cordata* having fishy smell, commonly known as fish mint, fish leaf, rainbow plant, chameleon plant, heart leaf, Chinese lizard tail and bishop's weed, Munsundari (Assamese), Simdalu (Hindi), Tokningkhok (Manipuri) and Ja Mardoh (Meghalaya), has been claimed to block the viral RNA dependent RNA polymerase [33]. Many Indian medicinal herbs have also been claimed to be promising therapeutic options of alternative medicine. Several published and unpublished reports have shown beneficial effects of many Indian herbs on COVID-19, like *Lycoris radiata*, commonly known as sunrise lily, hell flower, red magic lily, equinox flower and hurricane, commonly grown as ornamental plant, has shown beneficial effects on patients SARS CoV infection. Similarly, *Lindera neesiana*, known as *Siltimur* in Nepal

and is found in India Bhutan and Myanmar besides Nepal has shown potential therapeutic potential against COVID-19 cases. However, extensive research is warranted to explore the role of herbs and their products to prove their role against COVID-19. Ursolic acid, a product of Tulsi (Hindi), *Ocimum basilicum* and Raoulic acid from *Raoulia australis* have been claimed to have broad spectrum antiviral properties.

Challenges to control: The novel coronavirus (COVID-19) pandemic is becoming more challenging to break the chain of transmission globally day by day in absence of specific treatment and vaccine. Important community containment measures as advocated by WHO and several other agencies include social distancing, quarantine and isolation. For success containment in isolation, case detection is warranted at early stage before the viral shedding starts. It is evident in studies that secondary cases from infected person can be reduced if infected person is isolated within four days of onset of symptoms [34]. Quarantine involves movement restrictions with medical observations during the incubation period. Legally enforceable quarantine measure are the last resorts to restrict people movement in the community in order to bring down the R_0 to below 1. India and other third world countries as of now are in phase of enforced quarantine as a desperate measure to contain the spread and is the biggest challenge at present.

Since the lessons learnt from SARS in 2002-2003, the world is better prepared with new capacity building initiatives under WHO.

But still, several challenges have been identified in controlling the spread of COVID-19, like urbanization, people living in close proximity, high population density, widespread air connectivity and unrestricted air travel, which has massively swept continents within short span of time by expediting spread of virus across nations. The

long incubation period (2-14 days) and lower case fatality ratio are the major contributor in delay in recognition of the disease and implementation of effective control measures [35,36]. Lockdown is the last desperate measure to contain the community spread where the populations movement are restricted largely by law enforcement, which India is experiencing now.

The main challenge is high transmission of the disease compared to as observed for highly infectious diseases including SARS and MERS [37].

The rapid spread of the novel coronavirus in developing as well as developed countries is posing heavy burden on health care system, particularly in resources limited countries. The containment strategy is a challenge and becoming more difficult to enforce even in developed countries like USA, Italy, Spain and France. Previous coronavirus disease outbreak indicates that transmissibility also depends on various local variables such as density of population, hygienic practices and infection control standards which are not up to mark in most of the countries across the world.

Discussion

The world is experiencing outbreak of super spreading COVID-19 after other pathogenic CoV emergence such as SARS-CoV in 2002-2003 and MERS-CoV in 2012. Unpredictable spread of COVID-19, has posed serious threat to whole civilization of the world. The situation of COVID-19 outbreak has become alarming because the number of confirmed cases has grown exponentially and reached up to 462,684 and 20834 deaths till date [4]. The most affected nations such as USA, China, Italy, France and Iran are facing severe degree of community transmission. The case fatality ratio (CFR) is highest in Italy and lowest in USA. The reason of the highest fatality amongst the Italian citizens may be due to large proportion of elderly people with comorbidities and their

high socializing habits. Densely populated countries such as India and Pakistan are on the verge of alarming community transmission.

There are several reasons of exponential rise of cases including long incubation period, doubtful asymptomatic carriers and relatively low CFR.

The stability of the virus on the smooth surfaces also depends on temperature and relative humidity. One study from Hong Kong claimed that the low temperature and low relative humidity ambience in subtropical countries facilitates its transmission whereas tropical area (Malaysia & Thailand) with high temperature and high relative humidity restrained the transmission up to community level [15].

The necessary effective measures are needed to check the chain of transmission to bring the basic reproduction rate, R_0 below 1 globally and flatten the epidemic curve as much as possible by reducing community transmission.

Although as of now since no specific and effective treatments and vaccine available against COVID-19, the symptomatic management and lifesaving measures are of utmost importance combined with timely and accurate diagnosis. As of now, there is no conclusive research till date to help contain the virus. Several anti-HIV drugs like lopinavir, ritonavir, Nelfinavir and Remdesivir have been tried with some success citing same organization of the virus morphology [27-29]. Monoclonal antibodies coupled with chloroquine, arbidol and Baricitinib, a janus kinase inhibitor, have shown promising results and may be used as potential antiviral agents in future [30-32].

Several researches have shown promising effects of many herbs and their products on corona virus disease as well as in cases of COVID-19. These are known by various names depending on the language and their country of origin. Amongst all *Houttuynia cordata* and *Lindera neesiana*

have shown potential prospects of its being as anti COVID-19 agents [33].

The effective measures consist of proper hand hygiene practices, adherence to infection control standards and well-developed health care systems to treat patients and timely confirmation of cases which can help predict outbreaks. The containment strategy should be made to isolate the infected person until the risk of transmission has abated. Timely and adequate measures may turn the tide, even outbreak surge has reached to community transmission level. This is proved in china where combined physical distancing and travel restrictions have lowered ongoing transmission of the outbreak of COVID-19 in Wuhan [38]. Emergence of SARS in 2002-2003 demonstrated efforts put forth by many countries in controlling the outbreak within a short span of time and is evidenced by more than 4000 researches available online. But gaps in research still exist in terms transmissibility, stability other molecular mechanisms of the virus. A study done by Vincent CC Cheng et al, in 2007 predicted outbreaks of SARS like CoVs in future due their constant changing genotypes by recombination, and Chinese habits of eating exotic foods [39].

Conclusion

CoVs are enveloped, single stranded positive sense RNA viruses which are known to cause several human diseases including SARS and MERS. The nCoV shares around 70 – 80% of sequence homology with the already known SARS-CoV thus was named as SARS-CoV-2 by ICTV. India is one of the most affected countries with 0.3 cases per million population. Though it is a zoonotic disease, the primary mode of spread is person to person through respiratory droplets. The speed of transmission depends on basic reproduction rate. It seems that this virus gets inactivated at temperature above 38⁰C at a relative humidity of more than 95%. By the available facts it

seems that if community transmission is broken, it may not take serious toll in a country like India. Till date, there is no confirmatory research which can pinpoint the intermediate host involved in the transmission of the virus from animals to humans. The presentation of the disease ranges from flu to ARDS and MODS. But the most common clinical features, like fever (87.9%), fatigue (69.6%), dry cough (67.7%) and myalgia (34.8%). Many cases of fever with fatigue should be tested for CoVID-19 unless proved otherwise. There is no specific treatment available for the disease, legally enforced quarantine is the last resort to control the spread of CoVID-19. Despite several outbreaks of coronaviruses in humans in different forms, from SARS to MERS to latest CoVID-19, there is a huge gap in research on, specific vaccine and treatment.

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