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COVID 19: Outbreak, Structure and Current Therapeutic Strategies

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Abstract

The worldwide outbreak of COVID 19 is associated with novel coronavirus termed as SARS-CoV-2 by the international Committee on Taxonomy of Viruses (ICTV). As already World Health Organization had declared COVID 19 as international emergency as the disease spreading at alarming levels. This international emergency has triggered governments of various countries to take emergency measures to protect the public. As The virus spreading faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but it has lower fatality. Since information about this virus is rapidly increasing, it is necessary to remain updated. So in this context we present an overview of presently obtained information on virus structure, diagnosis, current potential therapeutics and preventive measures of this novel coronavirus.

Keywords: Novel Coronavirus, COVID structure, SARS CoV-2, Outbreak, pandemic.

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease mainly transmitted through the respiratory tract and has emerged by a novel Coronavirus, previously 2019-novel coronavirus (2019-nCoV), is currently designated as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The virus is highly homologous to the coronavirus (CoV) that caused an outbreak of severe acute respiratory syndrome (SARS) in 2003; thus, it was named SARS-CoV-2 by the World Health Organization (WHO) on February 11, 2020, and the associated disease was named Coronavirus Disease-19 (COVID-19) [1].

In Wuhan (Hubei Province, China) several cases of pneumonia patients of unknown cause were admitted to hospitals in December 2019. Cases were all linked to Wuhan's Hunan Seafood Wholesale Market, which trades in fish and a variety of live animal species including poultry, bats, marmots, and snakes [2]. The novel virus was identified from throat swab samples of patients, by the Chinese Centre for Disease Control and Prevention (CCDC) as the etiological agent in the reported cases [3]. On January 30, 2020, the WHO declared the outbreak of COVID-19 to be a Public Health Emergency of International Concern [4]. COVID-19 disease outbreaks caused significant mortality and morbidity in China compared to the rest of the world. As a new group of respiratory diseases, this disease recently taken a significant place in our daily practice, due to their higher rates of transmissibility, hospitalization, severity of disease, mortality and so on, we should pay more attention than past to prevention and treatment of coronavirus infection.

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Coronaviruse is spherical or pleomorphic, single stranded, enveloped RNA virus, covered with club shaped glycoprotein. The name "Corona" has been given due to the similarity of its spikes to a crown. Corona is a Latin word meaning "Crown". Coronaviruses has a history of causing numerous syndromes in humans and animals that includes Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV).

The International Committee of Taxonomy of Viruses, classified coronaviruses under the order *Nidovirales*, belonging to family *Coronaviridae*, subfamily *Coronavirinae*. Further the, *Coronavirinae* is divided into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.

There have six human coronaviruses (HCoVs) been identified, including the alpha-CoVs (HCoVs-NL63 and HCoVs-229E) and the Beta-CoVs {HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East respiratory syndrome-CoV (MERS-CoV)} [5]. Differences seen in Nidovirus families are in the number, type, and sizes of the structural proteins, cause significant alterations in the structure and morphology of the virions and nucleocapsids. The COVID-19 strains are genetically related with Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Surprisingly, the epidemiology of COVID-19 is also similar to SARS-CoV [6].

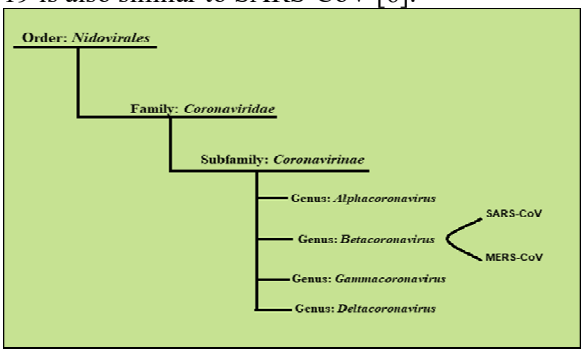

Fig. 1: Classification of coronaviruses

Outbreak of COVID-19

Since December 2019, number of cases of pneumonia with unexplainable cause occurring were alarmed the local hospital in Wuhan city, Hubei province, China. On 29th December, 4 cases were found to be linked to Huanan Seafood wholesale market. The local Center for Disease Control (CDC) then found additional patients linked to the same market after investigation, and reported to China CDC on 30th Dec 2019. The second day, 31st Dec, China CDC informed of the cases of pneumonia of unknown etiology to World Health Organization (WHO). Primary examinations revealed some environmental specimens were positive for COVID-19 in Huanan Seafood Market, Wuhan. Based on the WHO report, the marketplace was deemed positive for COVID-19, no specific association with an animal is confirmed yet.

The Chinese authority rapidly isolated a SARS-CoV-2 from a patient within a short time on 7th January 2020. On 10th Jan 2020, genome sequencing of the SARS-CoV-2 was first released and shared by China [7].

Initially the patients that contracted the disease had activities related to the market. But some confirmed COVID-19 positive patients did not visit the suspected market. Also health care workers are affected from the infected patients. This indicates that human to human transmission of COVID-19 is highly likely. As of 21st Jan, there are 270 cases were confirmed from Wuhan. On 23rd Jan, local Government has locked down the Wuhan city. On 30th Jan, WHO declared a "public health emergency of international concern" [4]. However, the worldwide situation of COVID-19 is worsening day by day and a large number of cases are being reported daily. The data analysis shows that the total number of COVID-19 confirmed cases has rapidly increased worldwide since 31st of December 2019. More than 197 countries has affected due to COVID-19 around the globe. Consequently, WHO declared COVID-19 a pandemic on 11th March 2020 [8].

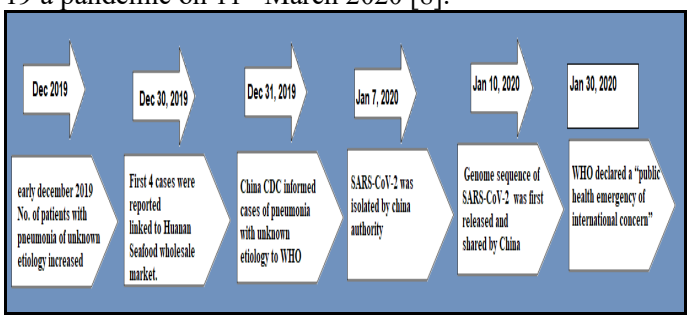

Fig. 2: key events in the early stages of the outbreak

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Transmission

Several reports have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. Person-to-person transmission occurs primarily through direct contact or through droplets spread by coughing or sneezing from an infected individual [9]. In addition, researchers also detected SARS-CoV-2 in stool samples, gastrointestinal tract, saliva and urine of the infected patients. In a small study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence that there is transmission from mother to child [10]. ACE2 (Angiotensin-converting enzyme 2) plays an important part in the immune systems, and SARS-CoV-2 infects host cells through ACE2 receptors causing COVID-19; hence, the individuals infected with SARS-CoV-2 face immune system disorders through progression of the disease [11].

Virion structure and main structural proteins

SARS-CoV-2 was first isolated in the bronchoalveolar lavage fluid (BALF) of three COVID-19 patients from Wuhan Jinyintan Hospital. Comparison of the genome sequences of the COVID-19, it showed that 2019-CoV closely related to SARS-CoV (about 79%) and MERS-CoV (about 50%) sequence identity. This indicates that 2019-CoV has a better sequence identity with SARS-CoV than the MERS CoV. Genome-wide phylogenetic analysis indicates that SARS-CoV-2 belongs to the Betacoronavirus genus, which includes Bat SARS-like coronavirus, SARS-CoV and MERS-CoV [12].

Like other Betacoronaviruses the SARS-CoV-2 virion is spherical or pleomorphic, with a diameter of 80–120 nm. It contains a non-segmented, positive-sense RNA genome of size ~32kb. The most prominent feature of SARS-CoV-2 is the club-shaped spike projections arising from the surface of the virion [13]. These spikes give them the appearance like a crown, prompting the name, coronaviruses. Coronavirus contain four main structural proteins. These are the spike (S), membrane (M), envelope (E) glycoprotein, Hemagglutinin Esterase (HE) and Nucleocapsid (N) protein. All E proteins and N proteins are present in all virions but Shorter projections made up of the hemagglutinin-esterase (HE) proteins are observed in some betacoronaviruses like SARS-CoV-2 [14].

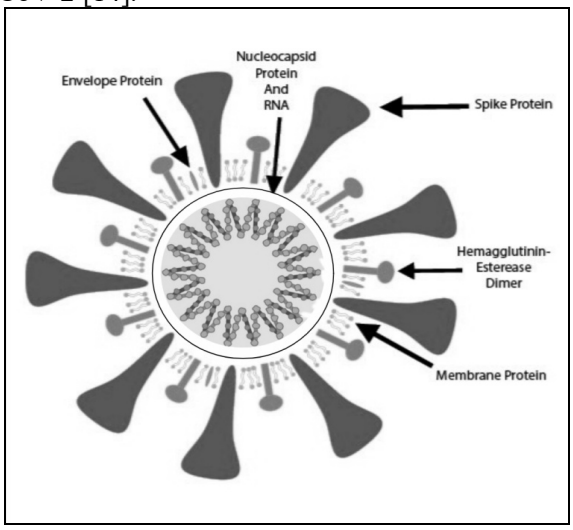

Fig. 3: Structure of SARS-CoV-2.

S Glycoproteins: Trimers of the spike protein gives distinctive spike structure on the surface of the virus giving a crown like morphology. In some betacoronavirus, the HE protein forms smaller spikes on the membrane. The S protein, utilizes an N-terminal signal sequence to bind to the C surface receptors in the plasma membrane of the host cell [15].

M Glycoproteins: (M) glycoprotein, the most abundant structural protein that gives the virion its shape and embeds in the envelope via three transmembrane domains. It has a small N-terminal glycosylated ectodomain and a larger C-terminal endodomain [16]. M protein may adopt two different conformations, allowing it to promote membrane curvature as well as to bind to the nucleocapsid.

E Glycoproteins: The E Glycoproteins are found in small quantities within the virion. The E protein has an N-terminal and a C-terminal ectodomain & endodomain resp. has ion channel activity. Coronavirus E proteins play a critical role in the assembly and release of virus [17].

N Proteins: Nucleocapsid (N) protein is heavily phosphorylated and binds to the RNA genome in a beads-on-a-string type conformation, forming the helically symmetric nucleocapsid within the viral envelope. It has two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA in vitro, [18] but each domain uses different mechanisms to bind RNA. The genomic packaging signal has

been found to bind specifically to the second, or C-terminal RNA binding domain. It plays a crucial role in virion structure, replication and transcription of coronaviruses [19].

Hemagglutinin-esterase (HE) proteins: (HE) protein is present in a subset of β-coronaviruses [20]. The protein acts as a hemagglutinin, binds sialic acids on surface glycoproteins, and contains acetyl-esterase activity. These activities are thought to reinforce S protein-mediated cell entry and virus spread through the mucosa [21].

The SARS-CoV-2 genome contains a 5′ cap structure along with a 3′ polyadenylated tail. It has been shown that the genome of SARS-CoV-2 contains a variable number (6–11) of open reading frames (ORFs). Two-thirds or about 20 kb of the genome of viral RNA, mainly located in the first ORF (ORF1a and ORF1b) translates two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins that interfere with the host innate immune response [22].

Physicochemical properties

As SARS-CoV-2 has a better sequence identity with SARS-CoV than the MERS CoV, most of the physicochemical properties of CoVs come from SARS-CoV and MERS-CoV. SARS-CoV-2 is most sensitive to disinfectants such as diethyl ether, 75% ethanol, chlorine, peracetic acid, and chloroform. It has been reported that SARS-CoV-2 can be inactivated by UV or heated at 56 °C for 30 min. It is more stable on plastic and stainless steel than on copper and cardboard. After application to these surfaces, viable virus was detected up to 72 hour [23].

Coronavirus Life Cycle

Attachment and Entry

The initial attachment of the virion to the host cell is initiated by interactions between the S protein and cell surface receptor(s). The S protein is composed of two functional subunits, S1 (bulb) for receptor binding and S2 (stalk) for membrane fusion [24]. Human angiotensin-converting enzyme 2 (ACE2) is a functional receptor attacked by SARS-CoV-2 for cell entry. Binding of S protein to the receptor leads change of conformational structure and the facillates entry of virus into the cell [25]. This S-protein–receptor interaction governs the tissue tropism of the virus. After binding, the virus next gain access to the host cell cytosol. After entering the cytoplasm, the virus particle releases the RNA genome. This genome is a single-stranded, non-segmented RNA virus with the largest known RNA genome.

Translation of Replicase and Assembly of the Replication Transcription Complex

The next step is, the translation of the replicase gene from the virion genomic RNA. The replicase gene encodes two large ORFs, rep1a and rep1b, which express two coterminal polyproteins, pp1a and pp1ab. The ribosomal frameshifting from the rep1a reading frame into the rep1b ORF causes due to utilizing a slippery sequence (5′-UUUAAAC-3′) and an RNA pseudoknot [26]. Occasionally the pseudoknot blocks the ribosome from continuing elongation, causing it to pause on the slippery sequence, changing the reading frame by moving back one nucleotide, a -1 frameshift. Autoproteolytic cleavage of pp1a and pp1ab generates having various functions 15–16 nonstructural proteins (nsps) [27]. either two or three proteases that cleave the replicase polyproteins encoded by Coronaviruses. They are the papain-like proteases (PLpro) and main protease (Mpro) are encoded by nsp3 and nsp5, respectively [28]. Many of the nonstructural proteins assemble at the replicase–transcriptase complex (RTC). This creates an environment suitable for RNA synthesis, and ultimately are responsible for RNA replication and transcription of the sub-genomic RNAs.

Replication and Transcription

The coronavirus replicase synthesizes full-length negative sense antigenome, by using the genomic RNA as a template [29]. The polymerase can also switch template during discontinuous transcription of the genome at specific sites called transcription-regulated sequences, thereby producing a 5’ nested set of negative sense sgRNAs, templates for the synthesis of a 3’ nested set of positive-sense sgRNAs [30]. Genome replication/transcription is mediated by the viral replicase and confines in the RTC. N protein is known to serve as an RNA chaperone and facilitate template switching. Importantly, the N protein also phosphorylated by glycogen synthase kinase 3 (GSK3), and inhibition of GSK3 was shown to inhibit viral replication in cells infected with SARS-CoV [31].

Another RNA-binding protein called heterogeneous nuclear ribo-nucleoprotein A1 (hnRNPA1) can also bind tightly to SARS-CoV N protein and potentially regulate viral RNA Synthesis [32]. Host RNA-binding proteins could also bind directly to untranslated regions (UTRs) of the coronavirus genome to modulate replication/transcription.

Virion Assembly and Release

The structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum–Golgi intermediate compartment (ERGIC) [33]. There, viral genome bud into membranes of the ERGIC containing viral structural proteins, which forms mature virions. When M protein is expressed along with E protein, directs most protein–protein interactions required for assembly of coronaviruses [34]. The S protein is incorporated into virions. Finally, viral structural proteins budded into the ERGIC are transported in smooth-wall vesicles and trafficked via the secretory pathway for release by exocytosis [35].

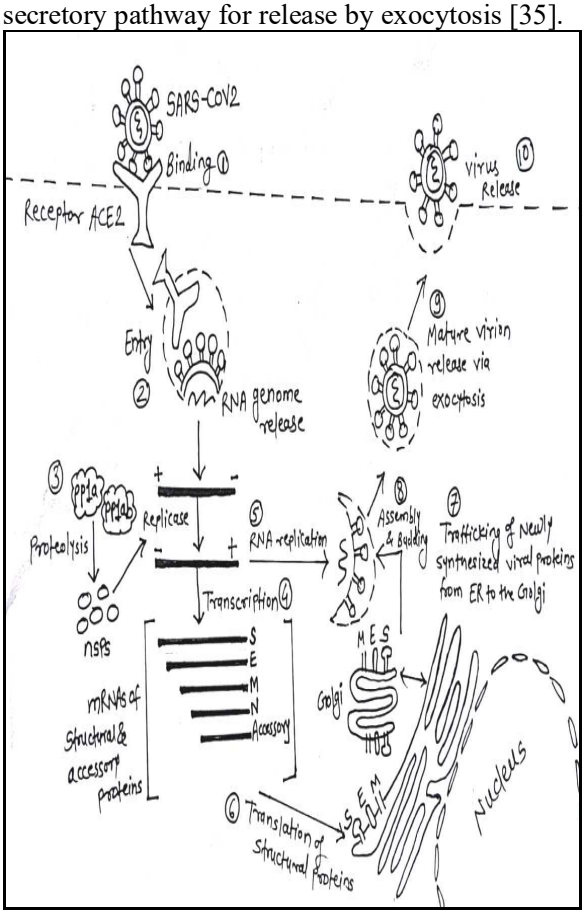

Fig. 4: Coronavirus Life Cycle

Clinical characteristics

The SARS-CoV-2 infection is common for people who are exposed to viruses or has immune weak functions; than others. Most of the infected patients had mild, moderate, or severe illness. COVID-19 includes severe Pneumonia followed by Acute Respiratory Distress Syndrome, sepsis and septic shock**.** Based on demographic study the percentages of the symptoms were 98% for fever, 76% for dry cough, 55% for dyspnea, and 3% for diarrhea; 8% of the patients required ventilation support [36].

The mean incubation period of SARS-CoV-2 is 1-14 days, mostly 3–7 days [37]. Laboratory findings are not remarkably different from those diagnosed with the other coronavirus infections, the most common finding is lymphopenia, together with low platelet count, decreased albumin levels and increased amino transferases, lactic dehydrogenase, creatine kinase and C-reactive protein levels [38]. The elderly and those with underlying disorders developed rapidly acute respiratory distress syndrome, septic shock, metabolic acidosis, even leading to the death.

Diagnosis

Any patient infected defined by having fever, sore throat and cough who has been in contact with confirmed COVID-19 infection. However cases may be asymptomatic or symptomatic.

Polymerase chain reaction

PCR is a process that causes a segment of DNA to be amplified, or multiplied many hundreds of times. SARS CoV-2 does not contain DNA but only RNA. Reverse transcription polymerase chain reaction (RT-PCR) technique uses reverse transcription to convert the extracted RNA to DNA [39]. When a throat swab collected from the infected person it treated which enhances breakdown of extraneous substances and allow RNA to be removed from the sample, then RT-PCR convert this RNA to DNA and then PCR technique is used to amplify the piece of resulting DNA in order to determine the genetic codes of SARS CoV-2.

This combined technique has been defined as real time RT-PCR or quantitative RT-PCR.

The detection of SARS-CoV using RT-PCR can have sensitivity of 50% to 79%, depending on the protocol used the sample type and number of clinical specimens collected [40]. Thus, it is

essential to enhance the sensitivity and detection rate of RT-PCR. Besides, it also has some shortcomings, includes certain biological safety hazards brought by the retention and operation of patient samples and long waiting time for results.

Imaging Technology

Although RT-qPCR is specific, but its low detection efficiency, false-negative rate cannot be ignored. COVID-19 has similar morphology to SARS-CoV and MERS-CoV therefore, COVID-19 has imaging findings found similar to those for SARS-CoV and MERS-CoV. CT scans should be one necessary auxiliary diagnostic method because of more sensitivity. A typical feature on CT initially shows bilateral multilobar ground glass pacities with a posterior or peripheral distribution [41]. However, CT scans also have some shortcomings, such as indistinguishability from other viral pneumonia and the hysteresis of abnormal CT imaging [42].

Immunological detection

It targets target viral antigens or antibodies as soon as possible. Currently, POCT of IgM/IgG and ELISA kits for SARS-CoV-2 have been developed, and shown higher detection rates than nucleic acid detection, but there is still no published article [43]. The sensitivity of SARS-CoV N-based IgG ELISA is significantly higher, but the issue of N based antibodies was implicated when five patients tested positive went through isolation of 2 weeks, then tested negative twicely, and again tested positive [44]. Hence, sensitivity is remains to be studied.

Current drugs under evaluation for the treatment of

No satisfactory treatment available for COVID-19 till date. There is no currently proof **for** antiviral agent for SARS-CoV-2 infection. Here, we discuss potential therapeutics available for the treatment of SARS-CoV-2.

Antiviral compounds

At the time, no effective antiviral agent has been confirmed. However, the drug options available from the clinical experience of SARS and MERS and other influenza virus have been used for the treatment.

Lopinavir/ ritonavir

The combination of lopinavir/ritonavir is widely used in the treatment of HIV infection. the use of protease inhibitor lopinavir/ritonavir with Ribavirin, a guanosine analogue, has a good therapeutic effect in treatment based on the experience gained from the SARS and MERS outbreaks [45]. Most recently, by Cao et al. the clinical trial of Lopinavir/ ritonavir (400 mg and 100mg, respectively, twice a day for 14 days) in treatment of COVID-19 has found that In hospitalized adult patients, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. in the lopinavir–ritonavir group, Gastrointestinal adverse events were seen more common [46]. Future trials with severe illness may help to enhance efficacy and safety of Lopinavir/ ritonavir treatment.

Remdesivir

Remdesivir a nucleoside analog has been identified effective in the control of COVID-19 in vitro. It shows broad-spectrum antiviral activity that inhibits the RNA-dependent RNA polymerase and block viral RNA synthesis, which has potential activity against a wide range of RNA viruses(including SARS/MERS-CoV) [47]. Antiviral activity of remdesivir and IFN-beta was found to be superior to that of lopinavir/ritonavir combination and IFN beta against MERS-CoV in vitro and in vivo [48]. As a candidate drug Remdesivir has been reported to treat the first US case of COVID-19 successfully. However, remdesivir is not approved by FDA nut available as emergency use authorization for the treatment of hospitalized adults and children. It also being investigated in clinical trials [49].

Arbidol

Arbidol, a broad-spectrum antiviral compound, small indole-derivative molecule showed inhibitory activity against SARS-CoV in vitro and recommended for clinical treatment [50].

Chloroquine and hydroxychloroquine

Chloroquine has been used to treat malaria for many years. The ACE2 membrane protein is functional receptor of SARS CoV which facillates entry of virus into cells by biding to the S-protein of virus. Chloroquine found to be a potent inhibitor of SARS-CoV through interfering with ACE2 [51]. Recently, Wang et al. have demonstrated that chloroquine is highly effective in COVID-19 infection. In addition, more than 100 COVID-19 patients has shown significant effective superior treatment in inhibiting the pneumonia, improving lung imaging and

shortening of disease. At present, the trial to determine the efficacy and safety of chloroquine is ongoing [52].

There are clinical trials to be conducted to test safety and efficacy of chloroquine or The hydroxychloroquine with or without aziithromycin in combination in treatment of COVID-19 patients are underway in the united states.

Hydroxychloroquine was reported to have more potent antiviral activity than chloroquine. Both chloroquine and hydroxychloroquine have immune modulatory effects which can suppress the immune response [53]. At present, the trials to determine the efficacy and safety of hydroxychloroquine are ongo

Convalescent Plasma

The collection of the blood from patients who recovered from a contagious disease to treat other patients suffering from the same disease or to protect healthy individuals from catching the disease [54]. It has also been reported that many convalescent patients donating plasma against SARS-CoV-2. One investigational treatment being conducted for COVID-19 is the use of covalescent plasma collected from individuals who recovered from a COVID-19. Use of Convalescent Plasma containing antibodies for SARS CoV has been studied in outbreaks of SARS and MERS epidemic [55]. Also, it has not yet shown be effective and safe as a treatment therefore, it is important to study safety and efficacy of convalescent plasma transfusion in COVID19 patients [56].

Monoclonal antibody therapy

The trimeric spikeb(S) protein of SARS-CoV-2 that mediates virus entry into the host cell can be neutralized by monoclonal antibodies [57]. A SARS coronavirus-specific human monoclonal antibody CR3022, can bind potently with the receptor-binding domain(RBD) of SARS-CoV-2. However, monoclonal antibodies can only recognize a single epitope, and the anti-infective effect may be limited [58].

Vaccines

Effective vaccines are essential and probably best option for tratement of COVID-19. Since SARS-CoV-2 S protein structure has been revealed, and These findings should provide the basis for further studies which enables the rapid and optimized vaccination development strategies [59].

Epitopes, mRNA, and S protein-RBD structure-based vaccines have been widely proposed and started. recently, on May 20, 2020 Moderna company announced that the company's experimental mRNA COVID-19 vaccine, known as mRNA-1273, has successfully finished its stage 1 of clinical trials and is among the leading candidates in the development of a possible vaccine for the novel coronavirus. The vaccine candidate being developed by Oxford University showed that vaccine was able to stop viral pneumonia from developing but could not prevent monkeys from catching infection. However, first phase of clinical trials of vaccine has already been conducted in April. It is notably fast development of an initial vaccine just weeks after identifying the SARS-CoV-2 genetic sequence.

Preventive measures

In general, there are no treatment options for COVID-19 at present. Due to the lack of experience with the novel CoV, supportive care to COVID-19 patients are provided by physicians, while attempting a variety of therapies that have been used these therapies including oxygen therapy, fluid management, and administration of antimicrobials for treatment of secondary bacterial infections to alleviate the symptoms and prevent end-organ dysfunction is currently recommended by WHO for suspected and confirmed cases requiring hospital admission [60]. Even plasma from recovered patients was proposed to be used for treatment. There are some particular medications are under investigation and are being tested through clinical trials in the United States and all around the world [61]. There are ongoing efforts of Pharmaceutical companies to develop antibodies and vaccines against the virus.

Standard precautions like wearing face Masks, hand hygiene, use of PPE, Working within 6 feet of a patient, safe waste management etc. should be followed at all time. Symptomatic contacts should be isolated for infection control, and diagnostic evaluation and management. Asymptomatic patients should be home quarantine for at least 28 days after the last exposure with daily monitoring for symptoms [62]. A positive case is to be managed at designated healthcare facility. These actions are

effective methods to lower the risk of infection as well as prevent the spread of the virus [63].

Conclusion

In conclusion, COVID-19 currently has emerged most intense and viral infection to many countries leading to a global pandemic. Several steps and precautionary measures has taken by many countries to ensure safety of the people, like hand hygiene, social distancing, isolation and quarantine. We still need to do more research and studies on the mechanism of virus, this helps to allow medical intervention to prevent disease. Rapid diagnosis, vaccines and therapeutics are most important interventions for the management of COVID-19 outbreak. At present all over world all scientist are in a race to find the solution to treat infection.

Several drugs such as Chloroquine, Hydroxychloroquine, Lopinavir, Ritonavir, Remdesivir, and Arbidol are currently undergoing clinical studies to test their efficacy and safety in the treatment of COVID-19 disease. The proper management of diet, nutrition, lifestyle, hygiene etc. are the sensible way to deal with the pandemic of SARS CoV-2.

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