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SARS-CoV-2, the Tiny Creature which Scared the Globe

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Abstract:

The 7th of January 2020, the novel *Coronavirus* was identified as the causative agent of COVID-19, a potentially deadly disease. The first cases were reported in Wuhan, Hubei province in China, but since the 11th of March 2020, a novel *Coronavirus* outbreak has been considered as a pandemic.

Belonging to Coronavirus family, SARS-CoV-2 is believed to be originated in bat then transmitted to humans by an intermediate animal host. Inhalation or touching infected droplets are the major ways to transmit the disease from human-to-human. Most of the patients are mild or asymptomatic. Symptomatic ones present mainly fever, sore throat, dyspnea, but in certain cases, it can lead to pneumonia, acute respiratory distress syndrome, or even multi-organ dysfunction.

Molecular detection methods are at high importance mainly rtqPCR. High-throughput sequencing of the whole genome can also be used, but it is very expensive. CRISPR Cas 12 has just got the initial validation as a detection tool of SARS-CoV-2. Serological tests and CT chest scan are also involved in the diagnosis. Treatment is symptomatic and supportive including isolation of patients. However, many drugs and vaccine candidates are under clinical experimentation. In this review, we prepared a quick summary of SARS-CoV-2 origin, transmission, clinical manifestations and management by highlighting the variable diagnostic methods and potential therapeutic agents, which may prevent the disease or fight the virus. It also provides a bird's eye view about the current outbreak status in Syrian Arab Republic in the Middle East.

Keywords: aAPC vaccine pathogen-specific, CRSPR Cas12, Hydroxylchloroquine, rtqPCR, SARS-CoV-2, Quarantine, Remdesivir

Introduction

The fifth of March of this year, the feelings of Muslims were shaken all over the earth after seeing the Holy Mosque in Mecca devoid of worshipers, as the Saudi authorities evacuated it to start sterilization procedures in anticipation of what is called the novel *Coronavirus*. Many events have been postponed, canceled or gone virtual such as Olympic games Tokyo 2020, Cannes Film Festival, Champions League and Europa League matches. What is happening in the planet?

The story started in December of last year. While people around the world were preparing for the new year, China in its turn was waiting for a big surprise. Four patients arrived at a hospital in Wuhan, the capital city of Hubei province with the first diagnosis for all as severe pneumonia.[1]

Doctors believed that those were weird medical cases as patients came to the hospital during the same period in December, three of them had a common exposure to the Huanan seafood wholesale market and they did not respond to the traditional treatment protocol of pneumonia after 3 to 5 days of antibiotic course so doctors decided to isolate them from other patients in the hospital.

On 31st December 2019, China raised the alert on the outbreak to the World Health Organization and Chinese authorities took drastic measures to contain the epidemic which reached initial accomplishments. Wuhan, as an epicenter of the disease, had been locked down. On the 7th of January novel *Coronavirus* was identified as the cause of this health problem. In spite of international warnings, novel *Coronavirus* passed borders without passport or visa and on March 11 2020,the WHO *declared novel coronavirus outbreak* a *pandemic* as it reached more than 200 countries with more than twelve million confirmed cases and more than500 000deaths. The USA and Brazil are now the new centers of the novel *Coronavirus* outbreak. 372 confirmed cases in Syriaamong them14 deaths until 9July 2020 at 12:38 pm.[2]The virus has spread rapidly all over the world, sending billions of people into lockdown in an attempt to slow down the transmission. This article overviewed latest information about COVID-19 focusing on variable ways to contain the pandemic by different diagnostic methods and potential therapeutic drugs and vaccine candidates against SARS-CoV-2.It also provided a bird's eye view about the current outbreak status in Syrian Arab Republic in the Middle East.

What Is Coronavirus?

Corona virus is a family involving positive single-stranded RNA (+ssRNA) viruses. They are distinct by their crown-like projections under electron microscopy due to spike proteins located on their surfaces, the name came from *coronam* the Latin word for crown.[3]

Corona family has a subfamily *called Orthocoronavirinae* which is categorized in four genera of Corona viruses: Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus. Moreover, the Betacoronavirus genus are classified into four lineagesA, B, C, and D.[4] From the genetic point of view, the gene sources of Alphacoronavirus and Betacoronavirus are probably bats and rodents Whereas, avian species appears to be the gene sources of Deltacoronavirus, and Gammacoronavirus. [4]

Seven members of Corona family are now known to circulate in humans. Four of which, HCoV-229E, and HCoV-NL63 (alpha CoVs); HCoV-OC43, and HCoV-HKU1 (beta CoVs of the A lineage) usually lead to mild respiratory diseases. Two other members for Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) and Middle East Respiratory Syndrome Corona Virus(MERS-CoV). Both give rise to severe respiratory diseases and are of bat origin crossed over to humans through an intermediate host, palm civet cats for SARS-CoVs and dromedary camels for MERS-CoVs. SARS-CoVs infected 8422 people with a fatality rate 11% (916 death) and the most of cases were in China and Hong Kong whereas MERS-CoVs reached 2494 persons with a high mortality rate of 34% (858 death) and most of the cases were in Saudi Arabia.[5,6]

The newest member of the corona family is the novel *Coronavirus*. Emerged first in Wuhan city and it continues to extend over new places on the earth.[7] On 11th February 2020, the WHO named the disease caused by this new CoV "coronavirus disease 2019 or COVID-19". The diameter of this tiny creature that scared the world is from 60 nm to 140 nm.[3]It belongs to beta category and its ssRNA genome composed of 29891 nucleotides, coding for 9860 amino acids and 29 proteins.[3]

After entering the cell, the virus started to translate genetic information carrying on its own RNA which contains 6-11 open reading frames (ORFs). ORF1a/b encodes two ploy protein chains, pp1 and pp2 involving 16 different non-structural proteins (NSP). Two of them act like scissors, snipping the bonds between the different proteins and liberating them to do their functions. The remaining ORFs translate structural and accessory proteins. Some of SARS-CoV-2 proteins have known

jobs as they are found in other corona viruses, but others are more mysterious, and some may do nothing at all. The S (Spike), E (Envelope), M (Membrane), and N(Nucleocapsid) proteins are the structural proteins of the virus. The S, E, and M proteins together constitute the envelop of the virus. The N protein packages the RNA genome in the envelope. The spike is a glycoprotein indispensable for SARS-CoV-2 to link to and fuse with the plasma membrane of the host cell.[8, 9]

According to genetic researches, this virus shares 89% of sequencesimilarity with bat SARS-like-CoVZXC21 and about 82% with human SARS-CoV sequence . For this reason it was called SARS-CoV-2.[10]

Genotyping data analysis of SARS-CoV2 from different confirmed cases revealed a mutation in the virus had been occurred in Chinese patients.[11]

Apparently, SARS-CoV2 seems to continue its evolution, two strain types of the virus have been reported. S type (~ 30%) and its derivative L type (~ 70%). The latter is evolutionarilymore contagious and aggressive than S type.[12]Researchers from the USAhave identifieda mutation at position 614 (Aspartate to Glycine) in spike protein which, according to their study, becomes dominant and makes the virus more contagious.[13] However, this study has not been certified by peer review. Another study at the University College London hasdiscovered 198 recurring mutations in the viral genome and concluded it is unclear whether the virus becomes more or less infectious.[14]Moreover, a research group at the University of Glasgow found that there is only one type of novel *coronavirus*currently circulating in the world.[15]

SARS-CoV-2 Origin

The exact origin of SARS-Cov-2 has not been identified yet. Three scenarios have been discussed by Anderson K et al., 2020. The first scenario suggests that a natural selection in a zoonotic host like bat and pangolin occurred before zoonotic transmitting to humans. It proposed that the virus had mutated within animal hosts then transmitted to humans leading to the primary animal to human transmission. Indeed, it has been shown that bat corona viruses (SARS-CoVs) exhibit elevated similarity to SARS-CoV-2. However, SARS-CoV differs in five out of six amino acids of spike protein at the binding site to human ACE2, meaning that SARS-CoVs will not be able to bind effectively to the humans' receptor binding domain RBD like novel *coronavirus*. On other hand, the pangolin corona virus shows high resemblance to SARS-CoV-2 in the RBD, including the six amino acids of RBD. Both bat and pangolin betacoronaviruses used in the studies do not have polybasic cleavage sites found in SARS-CoV-2.Anderson K et al. suggest that this difference is due to mutations, insertions, and deletions of corona virus genes within these hosts.

In fact, researchers could not confirm that Wuhan wet market is the root of SARS-CoV-2 until now due to the low number of samples used for the study that linked the market to SARS-CoV-2 outbreak.

The second possibility suggests that after transmission of novel *coronavirus* from bat or pangolin to humans, the virus mutated within the human body and acquired new characteristics (like the presence of polybasic cleavage site). It has been demonstrated that all SARS-CoV-2 share the same genomic features providing that they have the same ancestor that had these features too. The similarity of RBD between the pangolin corona virus and SARS-CoV-2 indicates that RBD was in the virus before reaching the human body, the inserted polybasic cleavage site was achieved during transmission from human-to-human.

The popular theory of SARS-CoV-2 derived from the previous virus escaped from the Wuhan laboratory has been excluded. RBD of coronavirus is optimized for binding to ACE2 in human cells, so it is improbable to be manipulated at the laboratory as Anderson K et al. concluded in their third scenario.[16]

Transmission and Epidemiology

The pandemic has been growing exponentially since the beginning of 2020. All ages are at risk to get the infection. The first cluster cases were in direct contact to

the Huanan live animal market and environmental samples taken from there, indicating that the virus originated from the market[17] and led to the fact that the main way of transmission was from animal to human. However, the number of people infected by the disease started to increase exponentially, some of them had not been to the Huanan seafood market inferring to the transmission from humantohuman.[18]

It is believed that the transmission of novel *coronavirus*occurs through inhalation of respiratory droplets through sneezing and coughing from symptomatic and asymptomatic patients and even before the onset of symptoms.[19, 20] The contaminated droplets can spread up to 4 meters from patients.[21]and settle on the surfaces. The virus can stay infectious there from hours to days in suitable conditions. Touching infected surfaces followed by touching eyes, nose or mouth is also another route of viral penetration into the body. Airborne transmission is also conceivable in case of prolonged contact with high aerosol concentrations inclosed area.[20] Feco-oral route is also discussed as the virus has been found in the stool.[17]

Common disinfectants such as hydrogen peroxide and sodium hypochlorite can destroy SARS-CoV-2 inless than one minute.[22]

Concerning the infection during pregnancy, there has been insufficient information whether the pregnant women are at higher risk of getting COVID-19 than other people nor if they are more subjected to have serious ailment. However, based on current data, pregnant woman has a similar risk as non-pregnant adults. Mother-to-child transmission of COVID-19 is implausible, but a newborn could be infected after birth through the human-to-human spread. Few neonates tested positive for novel *coronavirus* after birth. A small study found no traces of the virus in the vaginal fluid, amniotic fluid, breast-milk of women with severe COVID-19 infection.[23, 24]

According to data analysis realized by the China CDC and local CDCs of the first cases in Wuhan, the incubation period of the infection is between 3 to 7 days and could be prolonged to 2 weeks[25]; Recent data suggested COVID-19 is twice as contagious as previously thought. The basic reproduction number (R0) is 5.7, not 2.2 as it was first declared.[26]Taking into account, R0 for SARS-CoVs estimated to be <3[27]and for MERS-CoVs < 1[28].

Angiotensin-converting enzyme receptor 2 has been identified as the target receptor used by the virus to introduce to lung cells[29].

Clinical Manifestations

The clinical presentations of COVID-19 are generally mild and nonspecific. It could be symptomatic or may cause acute respiratory distress syndrome and may end with mal functioning of many organs. The common clinical manifestations involve hyperthermia, dry cough, dyspnea, myalgia, headache, fatigue, diarrhea, and conjunctivitis. Loss of sense of taste and smell has also been described. The British Association of Otorhinolaryngology (ENT UK) posted an online statement saying that many of COVID-19 confirmed cases had reported losing their sense of smell (anosmia) and taste with the absence of other symptoms.[30]

According to data analysis of affected patients in published series, 81% of cases were mild and recovered within two weeks.[31] In severe cases, the disease progressed rapidly with acute lung injury, acute respiratory distress syndrome (ARDS), septic shock and acute kidney injury. Patients at this stage presented very elevated levels of inflammatory cytokines like IL2, IL7, Monocyte chemoattractant protein 1(MCP1) and Tumor necrosis factor (TNFα).[7]

It has been shown that SARS-CoV-2 is very likely to infect elderly men with comorbidities. As its relatives SARS-CoV and MERS-CoV novel*coronavirus* infected men more than women.[32] This may be explained by the role of X-chromosome on innate and adaptive immunity.[33]Moreover, a recent study published in European heart journal has detected higher plasma concentration level of ACE2 in men comparing to women.[34] Patients with chronic underlying diseases such as cardio-cerebrovascular diseases, hypertension, asthma, and diabetes are at elevated risk of this viral infection.[18] Recently, obesity has been identified as a major COVID-19 risk

factor.[35]Out of 2000 ICU patients in France, 83% are overweight, according to Professor Jean-François Delfraissy, director of ANRS (France Recherche Nor & Sud SIDA-HIV Hepatites).[36]

Scientists at the University of British Columbia have found that smokers and chronic obstructive pulmonary disease patients COPD are more likely to get SARS-CoV-2 than nonsmokers as they have more ACE2 receptors.[37]

Infection with SARS-CoV-2 has been reported in newborns, infants and children. The infection was milder than in adults in the majority of cases.[38, 39]

However, official news about death cases among infants and young adults in Europe and the USA have been diffused lately. [40-42]

The reason for which some young, healthy people are dying from COVID-19 while others not may be revealed by genes. Many ongoing projects aim to analyze and compare the DNA from asymptomatic, mild and severe COVID-19 cases. Researchers at the University of Helsinki's Institute for Molecular Medicine in Finland suggest that differences might lie in genes encoding ACE2 or genes that support the immune response against the virus[43] or even those encoding particular blood types, type A individuals appear to get infection more than O ones according to a preliminary study from China.[44]

Several lines of evidence state that vitamin D support the immune system by modulation the adaptive and the innate immune system and plays an important role in defeating viral infections.[45] Recent results from Trinity College in Dublin found a link between vitamin D deficiency and the highmortality rate in patients infected by SARS-CoV-2 in Europe.[46] Another preprint statistical study on COVID-19 patients from Europe, Iran, USA, China , and South korea has found out that people with vitamin D deficiency are more susceptible to experience severe complications and are at height risk of death.[47]

Diagnosis

According to CDC, laboratory diagnosis is usually performed for those cases with clinical symptoms as fever, sore throat and cough who have been to regions of constant local transmission or communicated with probable or confirmed COVID-19 cases. Yet, patients might be asymptomatic or afebrile. As a suspect case has a positive molecular resultconsolidated with CT-scan outcome, clinical investigation, patient history, and epidemiological informationis considered as a confirmed case.

Molecular Detection

Two molecular diagnosticmethods for SARS-CoV-2 can be used, real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing. The reliable detection strategy is culturing the virus from patient's blood and high-throughput sequencing of the whole viral genome. However, the employment of this technology in clinical diagnosis is restricted due to the elevated cost. Thus, RT-qPCR is the mostwidely used and effective method to identify SARS-CoV-2.[48]

Upper and lower respiratory specimens can be taken for RT-qPCR detection. It has been recommended to target the ORF1ab and N gene regions by using specific primers and probes. A confirmed case has positive amplification for both target regions. However, the sensitivity of RT-qPCRvaries depending on the followed protocol, the type of specimen or the conditions of handling the samples. The highest sensitivity level 93% is from bronchoalveolar lavage fluid specimens, followed by sputum at 72%, nasal swabs at 63%, fibro bronchoscopebrush biopsy at 46%, pharyngeal swabs at 32%, stool at 29% and blood at 1%.[49] That is why taking samples from multiple sites are of high importance. Moreover, negative results do not exclude the infection with the virus and must not be utilized as the only basis for treatment. Negative outcomes must be consolidated with the clinical investigation, patient history and epidemiological information as recommended by the CDC. Excluding quality of the specimen, collection time of sample and technical problems, RT-qPCR is of considerable tool for the diagnosis of causative agents.[49]

In Syria, only the highly suspect cases are sent to designated reference

laboratories in Damascus, Lattakia, Homs and Aleppo.

Another molecular test, CRISPR-based lateral flow assay, which is developed by Mammoth Biosciences has just got initial peer reviewed validation. A CRISPR-Cas12 based method which is called the DETECTR assay for DNA Endonuclease-Targeted CRISPR Trans Reporter. It can specifically identify SARS-CoV-2 RNA for the Envelope and Nucleocapsid genes instead of patient antibodies. After performing this techniqueon the specimen PCR for the target gene region is applied, giving rise to a visual readout with a fluorophore. The assumed sensitivity is 90% and the specificity 100%.[50]

Serological Detection

Serology diagnosis for novel *coronavirus* is important to identify the number of COVID-19 cases, comprising asymptomatic and recovered cases. These tests can provide details about the prevalence of a disease in a certain area by detecting patients who developed specific antibodies against the virus. It includes RDT, ELISA and Neutralization assay.[51, 52]

Rapid Diagnostic Test (RDT)

It is basically a qualitative, small and portable lateral flow assay (positive or negative). It detects patient antibodies (IgM and IgG) against the N protein of the virus.RDT might utilizea sample from finger stick, saliva, or nasal swab fluids. The test shows colored lines indicating a positive or negative results. Cellex Inc has developed RDT that is approved by FDA for SARS-CoV-2 diagnosis.

Enzyme-linked Immunosorbent Assay (ELISA)

This is a qualitative or quantitative test which uses samples from whole blood, plasma, or serum. In this assaya viral protein of interest used to coat the plate such as Spike protein followed by incubation with patient sample. If the sample has antibodies (IgG and IgM) against the viral protein they form a complex together detected bysecondary antibody which produces a color or fluorescent-based readout. To date, all available ELISA kits are used for research purposes not for diagnosis of SARS-CoV-2.

Neutralization Assay

This test provides information whether a suspect case has effective and active antibodies against SARS-CoV-2, even after clearing the infection. In this test, viral infection of cells will be halted by antibodies of patient. It requires whole blood, serum, or plasma specimen from the patient.

Recently, FDA has approved the first diagnostic test utilizing home collective of saliva samples to be analyzed exclusively at Rutgers Clinical Genomics Laboratory.[53]

The Computerized Tomographic Chest Scan

CT-scan usually presents infiltrates, ground-glass opacities and sub segmental consolidation. These outcomes can be detected in asymptomatic cases as well, so CT imaging can be used to confirm suspect cases with negative molecular analysis.[54]

Another Laboratory Diagnosis Tests That Are NonspecificTo COVID-19

Platelets and white blood cell counts are usually normal or low. Lymphocyte countslower than 1000 has been linked to severe cases. High levels of CRP and ESR with normal levels of procalcitonin indicating a bacterial co-infection. The prothrombin time, creatinine, SGOT/SGPT are also at high levels.

Treatment

Nowadays, the world is desperate to find out strategies that can breakdown the rapid transmission of SARS-CoV-2and to discover effective drugs. Treatment is basically supportive and symptomatic after adequate isolation of patients to stop transmission to others. Mild cases are usually managed at home. Patients should keep hydration, nutrition and controlling pyrexia and cough. Non-invasive ventilation or mechanical ventilation are required for hypoxic cases. Incase of co-infection, antibiotics and antifungals are required. However, hundreds of clinical trials are ongoing to investigate the activity of drugs or vaccines against SARS-CoV-2. To date,

there are about 130 vaccine candidates in development and more than 200 treatments in consideration including antibodies, anti-viral agents, cell-based therapies and RNA-based treatments to fight the novel corona virus. Here are some examples :

EIDD-2801

An oral antiviral agent which blocknovel *coronavirus* in human airway epithelial cell cultures and multiple coronaviruses in mice.[55] EIDD-2801 blocks the virus by introducing mutations into the viral genetic material RNA. When RNA starts to make copies, the accumulation of damaging mutations will occur to a point at which the virus can no longer infect cells. EIDD-2801 seems to be effective against many RNA viruses. It could be taken orally early after diagnosis. The FDA gave a permission for human clinicaltrials to test this drug in the following months.

Favipiravir

Favipiravir or Avigan , a drug developed by Fujifilm Toyama Chemical in Japan asa treatment of influenza. It was approved as an experimental therapy as it seems to have promising results in treating mild to moderate infected cases with the novel *coronavirus*. 340 patients in China had been tested with this drug and it appeared to be safe and effective in the treatment of COVID-19. It blocks viral replication resulting in a short viral life cycle and improvement of the lung state of tested patients.[56]

Chloroquine CQ and hydroxychloroquine HCQ

These drugs have beenprimarily approved by The U.S. FDA to treat malaria,rheumatoid arthritis, and systemic lupus erythematosus. Elementary study in human and primate cell has demonstrated the activity of these drugsagainst SARS-CoV-2.[57, 58]Previous study showed that Chloroquine prevents the SARS-CoV virus from entering and replication inside human cells[59].Either of CQ or its less toxic derivative HCQ[60] is now given along with azithromycin[61].However, the CDC asked physicians to be vigilant when prescribing them to patients with chronic diseases, especially those with cardiovascular diseases. HCQ and azithromycin can cause torsade de pointe and increase in the risk of other arrhythmias and sudden death, stated by Association, the American College of Cardiology, and the Heart Rhythm Society on April 11[61]. A study on mice has shown that the combination of CQ or HCQ with metformincould be deadly[62].They are only to be used in clinical trials or emergency use programs.

Remdesivir

It was first tested in people with Ebola, but it could not beat theEbola virus. However, *In-vitro* studies have proven its efficacy in inhibiting the growth of SARS-CoV and MERS-CoV and preventing the infection of human cells with SARS-CoV-2.[58] It works by inhibiting the entire replication of the virus and it is given by intravenous injection. Remdesivir is approved by the FDA only for severe cases of COVID-19.

Kaletra

A combination of two antivirals, lopinavir and ritonavir that are protease inhibitors and have been used to treat HIV. Kaletra is now being tested against SARS-CoV-2, but data from China did not find any benefit when patients used the drug.[63]

Tocilizumab (Actemra)

The cytokine release syndrome or cytokine storm is the leading cause of death in some patients with COVID-19. As the immune system overreacts against the virus, it results in tissues damage and ultimately death. To calm down the immune activation, physicians are now testing Tocilizumab a monoclonal antibody and acts as immunosuppressant approved by the FDA fortreatment of rheumatoid arthritis and juvenile rheumatoid arthritis. It competes withinterleukin 6 (IL-6) for binding to IL-6 cell receptor. A clinical trial is now undertaken to detect the ability of Tocilizumab to improve the health status of adult patients with severe COVID-19 pneumonia.[64]

Losartan

Losartan is an antihypertensive drug, which works by blocking angiotensin-converting enzyme 2 (ACE2)

receptor used normally by angiotensin II to increase the blood pressure. Novel *coronavirus* binds to ACE2 receptor via spike and penetrates the cell. Since Losartan blocks this receptor, scientists thought it might help patients with COVID-19by prohibiting the virus from entering cells. Unfortunately, it has been elucidated that ACE inhibitors and angiotensin II receptor blockers (ARBs) including losartan, may contrarily stimulate the body to overexpress ACE2, thus increasing the capacity of the virus to enterthe cell.[65]An Italian study of 355 COVID-19 patients, revealed that three-quarters of dead patients had high blood pressure,so this is maybe one cause for their increased susceptibility.[66]However, a new study on patients with heart failure treated by ACE inhibitors or ARB did not show increased plasma levels of ACE2 after treatment.[34]

Ivermectin

A broad-spectrum anti-parasitic drug approved by FDA[67].*Invitro* studies have shown that this agent has a broad spectrum activities against viruses such as human immunodeficiency virus-1 (HIV-1), dengue virus (DENV), West Nile Virus,Venezuelan equine encephalitis virus (VEEV) and influenza. Recently, the FDA approved the *invitro* potential inhibition ability of Ivermectin against SARS-Cov-2.It seems like the drug prevents the translocation of the virus from the cytoplasmto the nucleus of the infected cells, resulting in normal and more efficient antiviral response in the infected cell.[68]

Umifenovir (Arbidol)

Developed in 1988 in Russia and it is used by Russians and Chinese to treat influenza A and B. It acts by inhibiting virus-cell membrane fusion. Umifenovir demonstrated an *invitro* activity against SARS-CoV and SARS-Cov2. [69, 70] Using Umifenovir in combination with Kaletra in COVID-19 patients improved CT scan results.[71]

Oseltamivir (Tamiflu)

A neuraminidase inhibitor, approved by the FDA in 1999 to treat influenza. Many clinical trials are currently evaluating the activity of Oseltamivir against SARS-CoV-2[72], though a Chinese study did not find any improvement in COVID-19 patients treated with this drug.[73]

Convalescent Plasma Therapy

An experimental therapy that uses plasma from COVID-19 recovered patients to treat severe clinical cases of COVID-19patients. The plasma is rich in antibodies specifically target the virus. Limited data showed convalescent plasma was well tolerated and improved clinical outcomes in treated patients.[74]

Vaccine

On 11thJanuary 2020, the genetic sequence of SARS-CoV-2 was published, eliciting global Research &Development activity to develop a vaccine fighting the virusMany candidates are currently at investigational or preclinical stages.[75] The most advanced vaccine candidates have entered the 1st phase of clinical trials are:

mRNA-1273developed by Moderna: Lipid nano particle system LNP-encapsulated mRNA vaccine coding for S spike protein. Recently, Moderna announced positive phase 1 trial data for the vaccine, which developed sufficient antibodies to neutralize the virus.

INO-4800 from Inovio Pharmaceuticals: DNA plasmid encoding S protein delivered via electroporation.

LV-SMENP-DCfrom Shenzhen Geno-Immune Medical Institute:Dendritic Cells DCs which has been modified with lentiviral vector to express synthetic minigene based on domains of specific viral proteins. It is administered with antigen-specific cytotoxic T-Cells CTLs.

Pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute: an artificial Antigen Presenting Cells aAPCs that has been modified with lentiviral vector to express synthetic minigene based on domains of certain viral proteins.

Moreover, scientists at the Institute of Biotechnology, Academy of Military Medical Sciences of China have already started the second phase of a clinical trial of Ad5-nCovan adenovirus type 5 vector vaccinethat expressesspike protein of SARS-CoV-2, according to Xinhua News Agency.[76]

Finally, traditional Chinese herbs had also found a place in the Chinese guidelines for treatment of COVID-19[77] such as:

-Fumigation with moxa in the room, 1-5 g/m^2 for 30 min per day.

-Medical tea: perilla leaf 6 g, Agastache leaf 6 g, dried tangerine or orange peel 9 g, stewed amomum Tsao-ko 6 g, and 3 slices of ginger. Soak the herbs in hot water and drink the water just like enjoying the tea.

-Chinese patent medicine: Huoxiang Zhengqi capsule or Huoxiang Zhengqi Shui (in half dose).

Prevention

Though prevention is a crucial strategy to get away from the disease, characteristics of SARS-CoV-2 make that difficult to achieve. COVID-19 has non-specific properties, one can transmit the virus before onset of symptoms or even without any symptoms appearance,a prolonged period of incubation, long duration of disease, and transmission may occur even after clinical recovery.

Yet, isolation of suspected or confirmed cases is of high importance. Peoples with close contacts or suspicious exposure should have a 14-day quarantine, starting from the last day of contact with COVID-19 patients or suspicious environmental exposure.[77] Good ventilationat home with enough sunlight help destruction of the virus.Patients should wear masks and practice good cough hygiene.In order to ensure continuity of care and stop transmission of the virus to other patients, healthcare workers must be vigilant and prudent as they are at great risk to be infected with SARS-CoV-2. They must be armed with N95 masks, gogglesand protective suits.Patients can be released from isolation as temperature slows down for at least 3 days and two sequential negative rtqPCR tests at1-day sampling interval.[78]At the society level, governments have urged to avoid gathering, keepsocial distancing and stick to essential activities only. Recommendations are diffused to use good cough hygiene by covering the nose and mouth with elbow or a disposable tissue. People should be advisedto practice hand hygiene every 15-20 min and clean surfaces, door grip, keys with suitable disinfectants. As an international response to the pandemic, almost all countries prohibited travel to or from their territories and are practicing lockdown for endemic cities.

Current Outbreak Status in Syria

The World Health Organization (WHO) considers the Syrian Arab Republic one of the high-risk countries in the Middle East region, taking into consideration challenges facing the health sector after more than nine years of conflicts. WHO supports the health system in Syria persistently to insure its preparations and response to fight SARS-CoV-2. WHO aims to reinforce surveillance and extending laboratory tests for early detection of infection in Syria. It provides healthcare workers with protective equipment to ensures proper case management and increases alertness and conducting risk communication.[79] It is quite surprising to know that till 9July 2020, the Syrian ministry of health reported only 372 confirmed cases with COVID-19 among them 14 deaths, most of cases were imported from other countries, though few days ago the ministry of health raised an alarm by announcing new confirmed cases without being in contact with people outside Syria.Indeed, nobody knows whether the reason behind the low number of COVID-19 cases is the insufficient materials used for diagnosis, resulting in underestimating the real number of infected cases, especially when you hear about hundreds of confirmed cases within the neighboring countries such as Lebanon and Jordan. Is there any benefit of BCG and MMR vaccines, used to be given to Syrian children, against SARS-Cov-2?. Are there special Arab genes making Arabs less susceptible to be infected by the virus?. Do lung cells of Arabs in the Middle East really express the ACE2 gene less than Europeans and East Asians by 1 to 1000 as unpublished Jordanian study has found?.[80] Is this situation partially due to the sanctions imposed by the USA government which have left Syria isolated from the world?. Does the danger condition limit traveling to Syria and reduce the spread of SARS-CoV-2 there?. Yet, no one has the

answer so as precaution measurements, officials in Syria have shut businesses, schools, universities, mosques, churches, and most government offices and stopped public transport. Quarantine is also considered for citizens in attempting to contain this health problem.

In conclusion, the novel *coronavirus* is a new challenge for the human being. Only time can inform us how this teeny creature will impact our lives in Syria and in the other parts of the planet.

In fact, despite all the distinct measures taken by different governmental authorities, SARS-CoV-2 continues its rampage around the globe, terrifies people without being terrified.

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