A Summary of Effective Management of COVID-19 in Iran Collaboration of Civil and Defence Forces

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Summary

The emergence of novel coronavirus hereafter named COVID-19 first observed in the Wuhan province of China rapidly transferred to other countries and soon became a pandemic. The first cases were officially announced on February 19 in Qom city, Iran. COVID-19 is a highly contagious viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pharmaceutical companies and research organizations are making efforts, to develop new treatments for this novel coronavirus. This review would discuss the management of the novel Coronavirus epidemic in Iran Collaboration of Civil and Defense forces from the beginning of the pandemic until 22 April 2020.

On 30 December 2019, a cluster of viral pneumonia cases of unknown origin emerged in Wuhan, Hubei Province of China which soon spread across the world. (1) From the first COVID-19 case in Iran, the Iranian President ordered health minister to set up a national committee for managing coronavirus epidemic. In his decree, President urged the Iranian Health Minister to use all his power to prevent the spread of coronavirus as well as uproot it from the country.

In response to the COVID-19 situation, Iran established a National Corona Virus Management Committee (NCVMC). The NCVMC consists of ministers of road and urban development, interior, education, science, tourism, and culture, as well as chief of staff of Iran's Armed Forces, head of budget and planning organization, IRIB chief, Iran's Attorney-General, head of pilgrimage and hajj organization, government spokesman and police chief. The committee is responsible to hold meetings, make policies in presenting services on health, treatment and pharmaceutical field, and inform people.

Understanding Biological Composition of COVID-19

A typical Coronavirus size is 65–125 nm in diameter and its genome pool contains a single-stranded RNA (Ribonucleic Acid) from 26 to 32kbs length. (2) Most coronaviruses contain three major proteins: the phosphorylated nucleocapsid protein (N); a small membrane-embedded glycoprotein (M); and a large club-shaped glycoprotein (S) which is projected spikes with 20 nm length. The M protein is synthesised on ribosomes bound to the endoplasmic reticulum and accumulates in the Golgi

apparatus. Researchers believed that the site of virus budding in the infected cell is affected by subcellular localisation of M protein to the Golgi. The S-protein involved in many of the biological processes of the virus, such as attachment to cell receptors, penetration, cell-fusion, is the major target for virus-neutralizing antibodies (3).

4 subgroups are reported for coronaviruses family including alpha (á), beta (â), gamma (ã) and delta (ä) coronavirus. (2).

The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19(4). Middle East respiratory syndrome coronavirus (MERS-CoV) (5), SARS-CoV (6) like COVID-19 cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and subsequently in a fatality (4).

Two prominent genomic characteristics have been reported for COVID-19. First, structural studies revealed that SARS-CoV-2 seems to have a great affinity for binding to Angiotensin converting enzyme 2 (ACE2) human receptors (7). ACE2 is highly expressed on the luminal surface of intestinal epithelial cells, it acts as a co-receptor for nutrient uptake, in particular for amino acid resorption from food (8). The receptor binding domain (RBD) in the spike protein is the most variable part of the coronavirus genome. Six RBD amino acids have been shown to be critical for binding to ACE2 receptors and for determining the host range of SARS-CoV-like viruses (7). In summary, the SARS-CoV-2 spike protein directly binds with the host cell surface ACE2 receptor facilitating virus entry and replication.

Second, the spike protein of SARS-CoV-2 has a functional polybasic cleavage site at the junction of two spike subunit (the S1–S2 boundary) through the insertion of 12 nucleotides, which additionally led to the predicted acquisition of three O-linked glycans around the site. This allows effective cleavage by furin and other proteases and has a role in determining viral infectivity and host range. These sites have not been reported in although other human betacoronavirus (7).

Currently, there are more than 11,346 full genome sequences of viruses from clinical samples around the World in https://www.epicov.org and Gene Bank with one full genome from Iran Accession ID: EPI_ISL_424349.

Coronavirus Cases in Iran

As noted till 23 April 2020, the country has set up 87000 laboratories. There have been 16,702 infected patients, of which 13,597 (81%) are in mild condition and 3,105 (19%) are in serious or critical condition. In terms of closed cases, out of 70,324 Cases — 64,843 (92%) have recovered / discharged and 5,481 (8%) have died.

Diagnostic

There are various methods to diagnose a COVID-19 infection. Diagnosis through CT imaging of the chest and counting white blood cell and or, preparation of a laboratory sample for definitive diagnosis by molecular methods.

Low-dose CT-scan, that is a widely available and almost inexpensive imaging test in Iran, is beneficial for the diagnosis of COVID-19 suspicious cases (9).

Sharif University of Technology engineers have provided a new diagnostic system by utilizing artificial intelligence algorithms via CT scans, this COVID-19 diagnostic system can be used when there is a large number of patients in hospitals or

there is no access to a radiologist. Such a system can double up as a doctor too (10).

Fig1. Mobile Biological lab of the Iranian Army

Islamic Revolutionary Guards Corps (IRGC) also unveiled Biodetection kits and Mobile Labs which is designed and manufactured in Iran and is capable of detecting the coronavirus named "MOSTA'AN" that is currently on evaluation process (11).

Fig 2. Mobile Lab Made By Basij.

The diagnosis of COVID-19 should be confirmed by molecular examinations the most usual one, reverse-transcription polymerase chain reaction (RT-PCR), or by gene sequencing of respiratory or blood specimens. Although these methods are crucial standard tools for COVID-19 detecting, they are time-consuming as well as may not be accessible widely (12).This delay in diagnosis and treatment subsequently results in a higher risk of infecting a larger population.

Several knowledge-based companies like Pishtaz Teb Company were successful to design and manufacture COVID-19 diagnostic kits (13).

Iran's Defense Ministry has begun the mass production of rapid coronavirus test kits (RT-PCR and serologic test). In late February, the Pasteur Institute of Iran approved the ministry's testing kit after examining them and comparing the result with foreign ones (14).

Anti COVID-19 Measures Assessments

a) Vaccine

The development of a safe and effective vaccine for this highly transmittable respiratory virus is an important epidemic control. To date, no efficient vaccine has been developed against COVID-19. Recombinant protein, mRNA, DNA and inactivated whole virus vaccines are being developed and some are now entering the clinical trial stage. The first COVID-19 vaccine in China is expected to be ready for clinical trials by the end of April, according to Xu Nanping, China's vice-minister of science and technology. Invio Pharmaceuticals plans to begin clinical trials on a coronavirus vaccine in April 2020. The most advanced candidates have recently moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute(4, 15-17).

Three independent groups are conducting research to produce a vaccine for COVID-19 in Iran and this country's health ministry concluded six contracts with knowledge-based companies for this purpose (18, 19).

The Head of IRGC's Baqiyatallah University of Medical Sciences, Brigadier General Alireza Jalali said that Baqiyatallah University focused the research on virus behavior that was the latest scientific material to be observed. Baqiyatallah University also focused on developing the Coronavirus vaccine, diagnostic kits and drugs which are complex and complicated processes.

b) Antibody

The first treatment for COVID-19 that anyone receives, is from their own immune system. Monoclonal antibodies are the major class of bio-therapeutics for passive immunotherapy to come up against viral infection. Monoclonal antibodies are a versatile class of pharmaceuticals that have been successfully used by the pharmaceutical industry. The Monoclonal antibody can perform efficient therapeutic intermediation with a highly specific treatment against a particular disease or agent (20).

Cytokine storm or inflammatory storm occurs by COVID-19 infection as a result of the release of proinflammatory cytokine including interleukins (IL) -6(21). In the biopsy samples at dissection from a patient who died from the severe infection with COVID-19, histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. Mononuclear inflammatory lymphocytes were seen in both lungs (22) that suggested the occurrence of such a phenomenon. Further, investigation on the immune characteristics of patients with COVID-19, showed that pathogenic T cells and inflammatory monocytes quick activation leads to a large number of cytokines production and ultimately inflammatory storm occur. Among them, IL-6 is the key cytokines, that cause inflammatory storm which may lead to increased alveolar-capillary blood-gas exchange dysfunction, notably impaired oxygen diffusion, and finally, result in pulmonary fibrosis and organ failure (23). Therefore, IL-6 might play a crucial role in the inflammatory storm and interfering with IL-6 by Immunomodulating drugs such as IL-6 inhibitors might be a potential therapeutic agent for severe and critical COVID-19.

One of the effective IL-6 inhibitors is Tocilizumab. It was effectively tested for the patients diagnosed as severe or critical COVID-19 in The First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital) and Anhui Fuyang Second People's Hospital. As a recombinant humanized anti-human IL-6 receptor monoclonal antibody, Tocilizumab can specifically bind IL-6 receptors and inhibit signal transduction (24). Tocilizumab rapidly resolved some of the clinical symptoms of COVID-19, such as fever and oxygen saturation while may decline the severity of the pulmonary complications of COVID-19, including respiratory failure, but there is no evidence that it has anti-viral potential (25). By Mach 11, the Iranian version of the Swiss-made "Actemra" has been used at one of Isfahan's hospitals (on **500** patients in different centers) and a relative improvement after 48 hours in the patient's symptoms has been observed. The mass production of this medicine was marketed in about three weeks (26, 27).

c) Antivirals

Antiviral treatments are crucially needed to diminish the burden on health-care systems worldwide. Effective therapeutics are expected to decrease fatality and hospitalizations. In the absence of a vaccine, antiviral agents could also be given to protect vulnerable populations.

Remdesivir (RDV, formerly GS-5734) is an investigational broad-spectrum small-molecule antiviral drug that its activity against RNA viruses in several families, including *Coronaviridae* has been determined (28). RDV is a phosphoramidate pro-drug of a 1'-cyano-substituted nucleotide analogue. Its triphosphate form (RDV-TP) resembles adenosine triphosphate (ATP) and is a substrate for viral RNA-dependent RNA polymerase (RdRp) enzymes (29). RDV showed a positive effect on 14 Americans who had severe acute COVID19. The first two of the five clinical trials testing have been done and RDV has completion dates in early April. Both phase trials are being run by Chinese groups (15).

One of the four drugs that Iran has joined with WHO (World Health Organisation) to complete the clinical phase is RDV. Iran has one of the biggest medical research capacities in the Middle East region and also among the Islamic countries has joined WHO clinical trials with 12 research teams in 100 patients (27, 30).

d) Convalescent Plasma

Apart from supportive care such as oxygen supply, no specific effective drug or vaccines for COVID-19 are available. Several agents, like RDV, are under research moreover, the antiviral efficacy of these drugs is not known yet (31).

Immunotherapy by transferring the convalescent plasma (CP) from recovered patients to patients suffered from COVID-19 may be effective in humans to overcome the virus infection (32). The use of CP was recommended as an experimental strategy during outbreaks of the Ebola virus in 2014 (33). In another study, 80 patients with SARS who were given CP have been associated with a higher rate of hospital discharge at day 22 from symptom onset compared with patients who did not receive the same (34). The early administration of CP from recovered patients that contains significant antibody titers may cause a reduction in viral load and disease fertility. Based on current findings a hypothesis raised that, utilizing a transfusion of the recovered patient could be profitable in cases infected with SARS-CoV-2. However, some crucial challenges need to be considered before using CP as a therapeutic option such as the availability of sufficient donors, clinical condition, viral kinetics, and host interactions of SARS-CoV-2 (32).

Two independent studies in china (245 patients in Xinhua and 10 patients in Wuhan) showed CP as a therapeutic option could potentially enhance the clinical issue through overcoming severe COVID-19 cases (35, 36). Some countries like Iran, Italy and the US are also using CP in clinical phase (37).

Masih Daneshvari Hospital in Tehran is the first medical center in Iran to collect plasma from recovered coronavirus patients to use as a possible treatment for the disease. 300 persons have donated their blood plasma, and the result was a 40 percent decline in the number of deaths due to COVID-19 (38). Now the trial phase continues in Baqiyatallah, Jondyshpoor, Mazandaran, Shiraz and Mashhad medical universities (27).

e) Cell-based treatment

Severe respiratory consequences of the COVID-19 pandemic have inspired a potential need for novel therapies (39). The most critical phase of COVID-19 is severe acute respiratory, thereby preventing this phase can be advantageous for the treatment and reduction of mortality rate (40).

Cell-based approaches, primarily using Mesenchymal stem (stromal) cells (MSCs), have determined as secure and efficient

options in cases that have acute respiratory distress syndrome (ARDS) (39).

There are many advantages for preforming MSC therapy in comparison with other treatments, such as: a) They are accessible and can be isolated from various tissues such as bone marrow and adipose tissues, including in umbilical cord, dental pulp, menstrual-blood, fetal liver, etc.; b) MSC are multipotent stem cells; c) They can be easily developed to the clinical volume within an appropriate period of time; d) MSCs can be saved for repeated therapeutic utilization; e) Clinical trials of MSCs so far haven't shown harmful reactions to allogeneic MSC; f) several clinical trials have reported that MSCs therapy is safe and effective. However, the cost-effective and speed of therapeutic preparation are capable topics for discussion regarding MSC-based therapy for COVID-19.

Recently, published reports have shown that some countries like China, the USA, Jordon, and Iran have put cell therapy in clinical trial phase. A case study reported in China on a female with an acute COVID19 syndrome. 21 days after the treatment with umbilical cord MSCs, results of laboratory tests and CT images indicate a significant improvement in her health condition (41). By clearing phase one of the clinical study, phase II started in China on 6 February 2020 with 10 cases between the ages 18-75 years. This phase is expected to be completed by September 30, 2020 (42). In Iran, the clinical trial phase of MSC therapy on COVID-19 infected patients has begun (27).

f) Other drugs

Research thus far has revealed more than 30 agents including natural products that may have potential efficacy against COVID-19. Some of these agents have been rapidly tested in the clinical phase and determined primary efficacy against COVID-19. Antivirals including interferon á (IFN-á), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol have been suggested by the National Health Commission (NHC) of China for experimental treatment of COVID-19 (43).

The sulfate and phosphate salts of chloroquine have both been commercialized as antimalarial drugs. Hydroxychloroquine has also been used as an antimalaria but is now being widely utilized to overcome autoimmune diseases such as rheumatoid arthritis. Notably, chloroquine and hydroxychloroquine are known to have side-effects. Lots of care must be taken while considering the effective dosage of this drug because chloroquine poisoning has been reported with cardiovascular disorders that can be life-threatening. Chloroquine and hydroxychloroquine use should be controlled with strict rules, and self-treatment must be forbidden (44). On February 17, 2020, the State Council of China revealed that chloroquine phosphate, an old drug for the treatment of malaria, had remarkable efficacy and suitable safety in treating COVID-19 associated pneumonia (45). This drug now is in phase IV of clinical trial and is being tested on 50 patients with confirmed severe COVID-19 conditions. The final result is expected by April-June 2020 (46).

As per the reports of Health ministry, Iran joined WHO for clinical trials of this drug on 24 March (30). On the other hand, Shahid Beheshti researchers have shown that rheumatologic patients who take 200 mg per day hydroxychloroquine, as well as the medical workers who received the same dose for prophylaxis against COVID-19, revealed that hydroxychloroquine with a 200 mg/day dose can have a relative prophylactic effect on COVID-19 (47).

Volunteers played a significant role

Even in Iran, the fear of COVID-19 led to mass hoarding of anti-corona products and masks. However, the country was quick to make up for those shortages. Almost all of the people reached out to volunteer in doing whatever could help to fail the disease. Volunteers offered services to the patients and medical staff, as well as aided in producing face masks, scrubs, and disinfectants. Many of these volunteers were housewives who sewed face masks and distributed them among the public and health workers. Furthermore, Iranian youth started producing disinfectants in universities, knowledge-based companies or religious places like a mosque. Many anti-corona products have been distributed among the financially weaker sections of the societies.

Many students and volunteers have also been working in hospitals and helping the medical staff. They help in feeding patients and sometimes encourage the patients and medical staff by reciting poems and songs. The medical staff has become so popular in Iran that they are being called "heroes of health." (48-53).

Knowledge-based companies, researchers come to the scene

Since Iran has been imposed with sanctions, obtaining drugs and equipment from other countries is costly and time-consuming. Therefore, Iranian researchers and companies have come together to make an effort to overcome these conditions.

Iran soon achieved the technology to produce kits for COVID-19 diagnoses that hit the market. Two types of diagnostic kits are now mass-produced by knowledge-based companies and defense ministry, the RT-PCR kits, 8 million of this kit are being produced per month; the other is serology-based kits — a total of 400,000 are being manufactured monthly and may reach up to 2 million (54). In addition, 40 advanced ventilators are manufactured daily in the medical equipment sector. This device is designed at a low-cost and easy-to-build technique by engineers in Tehran University Iran (55).

Some companies like Pars Nano are capable to produce high-tech Nanofiber masks. Other companies which produce Nano filters are altering their production lines to produce Nano masks and increase the capacity to manufacture from 100,000 masks each day to 300,000 in a few days. Iran is also planning to export masks to some countries soon (56, 57). Iran is also producing ozone generator (produce Ozone to replace carcinogenic disinfectants) and disinfection gate (58).

The Islamic Revolution Guards Corps (IRGC) and army

Soon after the spread of pneumonia secondary to COVID-19 in Iran, Armed forces mobile hospitals prepared for emergency admission of COVID-19 patients on February 26. Iran's two defense arm (army and IRGC) managed a national great biological defense exercise. The operation ran after the Iranian Supreme Leader Ayatollah Ali Khamenei, without evidence, which Iran had been subject to a "biological attack" following the outbreak of the virus (52).

All medical centers of the IRGC Ground Force were used at full capacity during the exercise and the disinfectant operations took place in 3,000 locations across the country, including 100 in the capital of Tehran. The exercise also involved 100 units of the IRGC Ground Force across 10 bases to carry out the cleaning operations (59).

On the other hand, Iran's Army established 300 medical centers in order to increase the

capacity of COVID-19 infected cases identification and prevent the spread of the disease (60). Army has transformed the Tehran exhibition center to a mobile hospital with 2000 beds in only two days (52).

Besides, these operations, dedicated attention was put towards manufacturing a great mass of diagnostic kit as mention before. They also started mass production of face masks, disinfectants, and protective clothes from the early days that the coronavirus pneumonia in Iran. They also unveiled advanced thermal cameras used for screening infected cases in crowded places (61).

Social and Media role for COVID-19 prevention

To decrease the rate of infection, Social Distancing Plan including not holding gatherings and prohibiting unnecessary travels was implemented (as early as 27 March and continue until April 3). According to the plan, inter-city trips will be prevented and only locals would be allowed to enter cities. Also, all parks, tour centers as well as any sites that might have large crowds, including pools, promenades, etc, was closed, even religious places like holy shires and mosques were closed (62).

Informing media from the first day of COVID-19 pneumonia, put lots of its attention on training people about the Coronavirus confrontation approach. In fact, national TV and the Media are in charge of increasing public awareness for all people and teams involved in the campaign against COVID-19 (52).

Response to Iran's coronavirus outbreak in late February, one of the government's first actions was to close schools and universities on March 5. The prolonged closure was a major challenge for students, parents and teachers. To decrease the effect of the school closures on the education system, Iran's Education Ministry introduced an online app, the Social Network of Students (Shad in Persian), and presents daily lessons for different grades on state TV. Two state TV channels in Iran are broadcasting educational programs. These two channels supported distance learning for mathematics, history, and social sciences that are taught by teachers (63, 64).

Conclusion

The global spread of coronavirus has caused many casualties, financial and social losses. However, Iran has used all its capacity, experience and knowledge of different sectors to combat the spread of the virus. Researchers, managers and the public have made a collective effort to combat the disease.

They have tried to turn the Corona crisis into a status for their scientific and social advancement. Due to long combat xperiences of defense forces consisting, the Army, Revolutionary Guards Corps (IRGC) and Basij or Mobilization Resistance and law enforcement police, Civil societies, volunteers, Red Crescent Movement against weapons of Mass Destruction especially Chemical and Biological warfare. All stages from surveillance to decontamination played an important part along with Medical and health staff to control the epidemic. After 41 years of various difficulties and crises from, 8 years of war, sanctions and hardships, Iran emerged as the most resilient nation in the world to fight any natural or man-made disasters or crisis.

Our knowledge and practical Experiences of Fighting WMD especially Chemical and Biological Weapons and Biological incidents due to more than 100,000 chemically injured military and Civilians and continuous threats

from enemies made nations defense forces to investigate and train to develop capabilities to fight against Biological incidents or crisis.

As Iranian leader said at the beginning of the epidemic we will turn this threat into an opportunity and as commander of the chief ordered the armed forces to use this environment as an example of Biological attack maneuver and try to manage the crisis and evaluate your capabilities and weakness and work hard to develop and expand Biodefense capabilities for future threats. Fortunately, effective collaboration between civilians and defense forces with the help of public Iran has been able to control the coronavirus.

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