Review

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A dossier on COVID-19 chronicle

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Abstract: The dissemination of the 2019 novel coronavirus (2019-nCoV) is presenting the planet with a new health emergency response or threat to health. The virus emerged in bats and was disseminated to humans in December 2019 via still unknown intermediate species in Wuhan, China. It is disseminated by inhalation or breaks out with infected droplets and the incubation period is between 2 and 14 days. The symptoms usually include high body temperature, cough, sore throat, dyspnea, low energy or tiredness, and weakness. The condition is moderate in most people; but in the elderly and those with comorbidities, it advances to pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure. Popular research work includes normal/low WBC with upraised C-reactive protein (CRP). Treatment is generally supportive and requires home seclusion of suspected persons and rigorous infection control methods at hospitals. The Covid-19 has lower fatality than SARS and MERS. Among the proposed therapeutic regimen, hydroxychloroquine, chloroquine, remdesivir, azithromycin, tocilizumab, and cromostat mesylate have shown promising results, and the limited benefit was seen with lopinavir–ritonavir treatment in hospitalized adult patients with severe COVID-19. Early development of the SARS-CoV-2 vaccine started based on the full-length genome analysis of severe acute respiratory syndrome coronavirus. Several subunit vaccines, peptides, nucleic acids, plant-derived, and recombinant vaccines are under pipeline. Research work, development of new medicines and vaccines, and efforts to reduce disease morbidity and

mortality must be encouraged to improve our position in the fight against this disease and to protect human life.

Keywords: corona; COVID-19; dissemination; fatality; incubation.

Introduction

The biggest challenge to public health is the current epidemic of respiratory disease that earned the name Coronavirus disease 2019 (Covid-19). In December 2019, a bunch of pneumonia cases, resulting from lately detected beta coronavirus, occurred in Wuhan, China. On February 12, the World Health Organization (WHO) described it as the 2019-novel coronavirus (2019-nCoV) that spread rapidly across the world [1, 2]. On 3 January 2020, the incident was labelled as the Public Health Emergency of International Concern (PHEIC). The fatality ratio was much lower than the SARS of 2003, but the dissemination has been substantially higher. As of November 30, 2020, the total number of Covid-19 cases was 63,083,565 with a total death of 1,465,309. India reported 94,32,129 confirmed cases as of now with 1,37,177 deaths and 88,46,475 recoveries with higher mortality and morbidity among elderly people. The fatality rate is approximately 2–3% according to the currently reported cases [3].

In response to Covid-19, many countries used a mix of confinement and prevention measures to postpone major disease outbreaks and raised hospital bed demand. Activities to achieve these objectives differ and are established on national risk evaluation that involves the approximate number of patients needing hospitalization, hospital bed availability, and ventilator support [4–6]. Most national contingencies include self isolation or quarantine; promotion of public health measures, including hand-washing, respiratory hygiene, and social distancing; readiness of health systems advent of critically ill patients needing isolation, oxygen, and mechanical ventilation; improving health facility for the prevention and control of diseases, postponing or cancelling large-scale public meetings [7–9].

This article is aimed to provide a brief review of current knowledge of the Covid-19 and summarize important clinical features as documented at present.

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Origin and transmission of Covid-19

In December 2019, adults in Wuhan began to pose extreme pneumonia of unknown origin to nearby hospitals. Numerous earliest cases were usually introduced on the wholesale market for seafood, where live animals were often traded. The monitoring devices were activated and respiratory samples for etiological studies were sent to reference labs. China informed the WHO of the outbreak on December 31st, 2019, and on 1st January seafood market was closed. The virus was reported to have 95% homology to bat coronavirus and >70% similarity to SARS-CoV-2. Studies evaluated that the number of reproduction (R_0) was approximately 2.2 [10] or even more (range from 1.4 to 6.5) [11, 12], which is rapidly rising through human-to-human dissemination.

During the Chinese New Year, the outbreak was fuelled by massive Chinese migration. Cases were registered in Provinces of China, and in people coming back to Wuhan from other countries [13].

Spread of Covid-19 in India

India reported its first Covid-19 case in Kerala on January 30, rising to three cases all of which were students returning from Wuhan, China. The remaining of February saw no substantial rise in incidents. On 6 March, 28 new cases were reported, including those of a group of Italian tourists with 14 members infected [14].

The dissemination intensified during March, followed by several cases across the world [15].

Confirmed cases crossed 100 on 15 March, https://en.wikipedia.org/wiki/2020_coronavirus_pandemic_in_India - cite_note-28 82,990 by 15 March, 100,000 by 15 July and 94,32,129 by 30 November with 1,37,177 deaths and 88,46,475 recoveries.

Global impact of Covid-19

At first, the assumption was that only in China would the Covid-19 be restricted. It subsequently escalated with people travelling all over the globe. The economic hardship was serious as people were compelled to stay at home, and the impact has been felt in different economic sectors with the travel ban, cancellation of sports activities, a ban on mass congregation concerning activities, and the recreation business [16].

As of November 30, 2020, the Covid-19 outbreak has been confined to around 210 countries. The virus has infected 63,083,565 people worldwide with a total death of 1,465,309. The countries worst affected include the United States, Brazil, and India.

Regional data published by the WHO on the expansion of the Covid-19 suggest that the highest number of Covid-19 cases is in Europe followed by America and Asia [17].

It is projected that the international economy could decline due to the coronavirus pandemic, the decrease could be 1%, the UN said, admonishing it can shrink even more if the economic downturn restrictions are expanded without appropriate budgetary responses.

Coronavirus structure and life process

Coronavirus is an enveloped globular or changeable particle with mono filamentous (positive sense) ribonucleic acid (RNA) and a capsid nucleoprotein consisting of a protein matrix [18, 19]. The envelope holds an expression of a glycoprotein projection formed by a club [20]. Many coronaviruses often contain a protein called esterases of hemagglutinin (HE) [21].

Coronaviruses have the genetic material (26.4–31.7 kb) of all known G + C containing RNA viruses ranging from 32 to 43%. Varying open reading frames (ORFs) between the various retained genes and downstream of the nucleocapsid gene in different lineages of coronaviruses are present. The viral genetic material includes a distinctive N-terminal inside the protein spike. For all coronavirus proteins including S, E, M, and N occur in the order 5–3' [22, 23].

Coronavirus contains six ORFs in its genetic material. Excluding gamma coronavirus which encodes nsp1, the first ORFs (ORF1a/b), approximately two-thirds of the entire genome length encode 16 different nsps [24]. Polypeptides are transformed into 16 nsps by virally encoded protease like chymotrypsin (3CLpro) or key protease (Mpro) or proteases like papain. Both the proteins are translated of CoVs from sgRNA. Spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins are encoded on the 3'-terminus by 10, 11 ORFs. There are different proteins that CoVs encode such as 3a/b protein, HE protein, and 4a/b protein. These proteins cause genetic material preservation and replication [25].

The coronavirus is composed of 3–4 membranes of viral proteins. There is an interaction joining the envelope protein that determines the composition and formation of the

membrane of the coronavirus. In the existence of tunica-mycin coronavirus grows and produces spike-less, non infectious virions that do not contain S but contain M [26–28].

Entrance mechanism of human coronaviruses

Coronavirus entrance is dependent on proteases like human airway trypsin (HAT), cathepsins, and transmembrane protease serine 2 (TMPRSS2) [29].

SARS-CoV-2 spike protein contains a coronavirus structure that expresses certain polypeptides, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, glycoprotein, and accessory proteins [30–33]. In the region of RBD, the spike protein SARS-CoV-2 holds a 3-D structure to support the forces of the Van der Waals. The residue of 394-glutamine in the SARS-CoV-2 region is identified by the residue of essential lysine 31 on the ACE2 receptor of humans [34].

SARS-CoV-2 begins its biological cycle inside the cell of the host when ACE2 receptors to S protein [35, 36]. After binding with the receptor, the S protein's conformation changes and facilitates envelope fusion with the biological membrane with the help of the endosomal channel. SARS-CoV-2 then releases RNA into the human host cell. RNA is transformed into viral replicase polypeptides pp1a and 1ab, which are broken by viral proteinases into small fragments. The polymerase generates subgenomic mRNAs via interrupted transcription, eventually converting them into appropriate proteins. Subsequently, viral proteins and RNA gets collected in endoplasmic reticulum (ER) and Golgi virions and then carried with the help of vesicles and thrown from the cell [37–42].

Mode of transmission of Covid-19

COVID-19 virus is transmitted between humans via minute respiratory droplets and communication paths. The occurrence of droplet transmissions takes place in a person who is in close contact (within 1 m) with someone who has respiratory symptoms (e.g., coughing or sneezing) and is thus, at the risk of exposure to potentially infectious respiratory droplets through his/her mucosae or conjunctiva. An infected individual releases fomite into the immediate environment which leads to the transmission of the virus [43–46].

Another mode of transmission observed is airborne transmission which is possible particularly in situations where aerosols are generated include:

- Bronchoscopy
- Endotracheal intubation
- Nebulized treatment
- Manual ventilation preceding intubation
- Tracheostomy
- Cardiopulmonary resuscitation
- Patient being disconnected from the ventilator

Some research indicates that Covid-19 affects bowel movement as well, sometimes manifesting in feces as well. However, only one research till date has been able to extract the virus from a single stool specimen, on the other hand, the fecal–oral transmission of the virus has not been reported till date [47].

Human to animal transmission

The first documented case of an animal infected with COVID-19 is believed to be a tiger in the Bronx Zoo, in New York City. The National Veterinary Services Laboratory in Iowa confirmed the test result. The tiger is thought to be infected by an asymptomatic zookeeper [48].

Pathogenesis

Abnormal respiratory findings, an unusually high number of leucocytes and a raised level of proinflammatory cytokines in the plasma are traits exhibited by patients who have been diagnosed with the virus. A particular case report of a Covid-19 patient indicated that he suffered symptoms of cough, raspy breathing sound in both lungs, and a body temperature of 39 degrees Celsius. The infection was confirmed by using the sputum of the patient which yielded positive results in the real-time polymerase chain reaction. Studies conducted in the laboratory showed leukopenia with a leukocyte count of 2.91×10^9 cells/L, out of which neutrophils comprised 70%. Severe pneumonia, RNAemia coupled with the occurrence of ground-glass opacities, and acute cardiac injury are the main pathogenesis of the respiratory system targeting virus. A Covid-19 patient has a significantly high level of cytokines and chemokines. In extreme cases, which require ventilation in the intensive care unit, high levels of proinflammatory cytokines were reasoned to encourage the severity of the disease [49–53].

Factors affecting virus pathogenesis

Co-morbidities include both cardiovascular and cerebrovascular disease and diabetes. A few of the other disorders observed and reported in COVID-19 patients are cellular immune deficiency, coagulation activation, myocardial injury, hepatic, and kidney injury. Most of serious illness and death cases have reported findings of lymphopenia. A point to take note of is that these findings are comparable to those suffering from SARS during the 2003 epidemic [54].

Several forms of S protein-dependent vaccines and antiviral drugs have been previously tested. Vaccines can be based on the S protein include full-length S protein, viral vector, DNA, recombinant S protein, and recombinant RBD protein. Considering that the antiviral therapies dependent on S protein are included in the *in-vitro* analysis as RBD–ACE2 blockers, S cleavage inhibitors, fusion core blockers, neutralizing antibodies, protease inhibitors, S protein inhibitors, and small interfering RNAs. The receptor-binding domain of SARS-CoV-2 exhibits a higher affinity for ACE2 [55–59].

Despite belonging to the ACE family of dipeptidylcarboxy dipeptidase, the angiotensin-converting enzyme (ACE) and its counterpart ACE2 have varied physiological functions. ACE2 acts as the COVID-19 binding site. Based on the information, the ACE2 acts as the COVID-19 binding site, Gurwitz proposed the use of accessible angiotensin receptor 1 (AT1R) blockers, to minimize the severity of COVID-19 infection with the help of a therapeutic drug such as Losartan. To understand the rate of virus spread among humans, it is essential to determine whether COVID-19 is mutating to strengthen its binding with human receptors for infection, given its rate of mutation. Any improvement in the COVID-19 series that could make it more effective for people to transmit, could also improve its virulence [60].

Diagnostic criteria

The identification of nucleic acids in the screening of nasal and throat swabs or other respiratory tract samples by polymerase chain reaction (PCR) in real-time is considered the most accurate and sought-after clinical diagnostic tool for Covid-19 [61, 62].

Complications

Complications that arise with infection are ARDS, arrhythmia, acute kidney injury, acute heart injury, liver

disease, and secondary infection. The severity of the disease leads to a low clinical outcome. The elderly are adversely affected due to the quick growth of the virus in that age group [63]. On the other hand, young children also seem to be vulnerable to this virus with over 50,000 reported cases, of which the youngest was just 30 h old [64]. Therefore, the elderly and neonates require greater care and attention because of their immature or poor immune systems [65–69].

Treatment

As with any other virus, treatment is solely for the symptoms affecting a patient and requires respiratory support according to the diagnosis and treatment of pneumonia caused by COVID-19 and extracorporeal membrane oxygenation (ECMO) was suggested by the WHO for patients with refractory hypoxemia [70].

Currently, there is no antiviral drug or vaccine that has been approved by the WHO. The real challenge that we face is the development of an effective and reliable vaccine which ideally should be a wide-spectrum treatment. This process is a painstakingly long, combined effort of research and development. In the meantime, what we can do is systematically screen preexisting drugs to assess their activity against the Covid-19 virus.

Remdesivir, which is an antiviral drug, has been found to be successful in the treatment of a wide range of RNA viruses due to which Holshue et al. formally announced unprecedented breakthroughs in the treatment of a Covid-19 patient. After Holshue et al. [71], Xioa et al. [72] showed through their research effective *in-vitro* control of 2019 nCoV infection. Chloroquine has been found to have an immunomodulating function that could effectively inhibit the virus *in-vitro* [73]. The clinical trials have strongly shown its potential in COVID-19 patients [74, 75]. An antiparasitic drug called ivermectin has been noted to have inhibited the SARS-CoV – two from replicating *in-vitro* [76]. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that binds to the IL-6 receptor with high affinity. An initial observational study conducted by Xu et al. [77] has shown favorable results for tocilizumab therapy [78, 79]. Convalescent plasma has been widely used to boost the endurance of patients [80–82]. Some blood centers have started assembling plasma from patients who have recovered from Covid-19, with hopes that their plasma contains antibodies that are able to resolve the virus in infected individuals. Corticosteroids, particularly methylprednisolone, have been suggested as an adjunctive agent in Covid-19 treatment. Corticosteroids have been successful in treating severe pneumonia and lung damage because of their anti-

inflammatory nature [83]. Camostat mesylate is a protease inhibitor, successful against trypsin, plasmin, kallikrein, and thrombin [84–86]. It also inhibits the serine protease TMPRSS2 [87]. Based on the current understanding of the SARS-CoV-2 infection mechanism, TMPRSS2 facilitates the activation of the viral S-protein and subsequent membrane fusion and entry. This makes camostat mesylate a possible pharmacological agent to inhibit SARS-CoV-2 entry into host lung cells, averting initial infection. SARS-CoV-2 utilizes the ACE2 receptor for host cell entry, making it a potential target for COVID-19 pharmacotherapy [88]. This has invigorated debate within the scientific community, as according to some postulate blocking ACE2 receptors with ACE inhibitors and ARBs may lead to a low performance by upregulating the receptors and increasing viral entry [89]. Conflicting *in vitro* studies make it unclear whether these agents are therapeutic or harmful in COVID-19 patients [90] (Table 1).

Vaccines

More than 180 vaccine candidates, based on several different platforms are currently in development against SARS-CoV-2 the WHO maintains a working document [138] that includes most of the vaccines in development [139]. The platforms can be divided into ‘traditional’ approaches (inactivated or live-virus vaccines), platforms that have recently resulted in licensed vaccines (recombinant protein vaccines and vectored vaccines), and platforms that are yet

to result in a licensed vaccine (RNA and DNA vaccines) [140] (Table 2).

Few vaccines have been authorized. Pfizer/BioNTech’s BNT162b2 received temporary authorization from the UK Medicines and Healthcare products Regulatory Agency on 2 December. Sputnik V – formerly known as Gam-COVID-Vac and developed by the Gamaleya Research Institute in Moscow – was approved by the Ministry of Health of the Russian Federation on 11 August.

Prevention

The focus of preventive measures is to optimize protocols for infection control and isolation which are clinically approved and have clinical care. Close interaction with patients, farm animals, and wildlife has all been warned against by the WHO. To avoid aerial transmission of the virus, cough and sneezes must be covered by the general public, especially in the outdoors. Regular handwashing with antiseptic soap and water is still the most effective way of prevention [141], but due to the shortage of water in densely populated urban areas hand sanitizers can be used as a preventive measure. Immune-compromised patients are strictly advised to stay indoors and avoid public gatherings. The department of emergency medicine must be given the authority to put in place strict hygiene-based initiatives to curb the spread of infection. Personal protective equipment kits [142, 143] must include N95 masks

Table 1: Possible treatment of Covid-19 by using existing drug.

Drug	Mechanism	References
Antiviral agents		
Remdesivir	RNA-dependent RNA polymerase inhibitor	[71, 91–95]
Lopinavir, favipiravir, and ritonavir	RNA-dependent RNA polymerase inhibitor	[75, 96–100]
Oseltamivir	Neuraminidase inhibitor	[83, 90, 101]
Umifenovir	Spike protein/ACE2 membrane fusion inhibitor	[83, 102–106]
Chloroquine and hydroxychloroquine	Chloroquine suppresses developing and releasing of TNF- α and IL-6 an inhibitor of autophagy that interrupts viral replication	[73, 107–112]
Ivermectin	Unclear maybe by inhibiting IMP α / β - mediated nuclear import of viral protein.	[76, 113, 114]
Immunomodulatory agents		
Tocilizumab	Tocilizumab is a recombinant humanized antihuman IL-6 receptor monoclonal antibody that binds to the IL-6 receptor with high affinity.	[78, 79, 115–118]
Interferons (ex. IFN α and IFN β)	Activate interferon-stimulated genes: Interfere with viral replication, immunomodulatory effects	[106, 119–125]
Adjunctive agents		
Azithromycin	Antibacterial; used in combination hydroxychloroquine for synergistic antiviral effect.	[126–130]
Corticosteroids	Cytokine gene expression Inhibitor	[83, 131–133]
Miscellaneous agents		
Camostat mesylate	Serine protease inhibitor	[84–87, 90, 102]
ACE inhibitor/ARB	ACE inhibitor; inhibit formation of angiotensin II ARB; angiotensin II receptor antagonist.	[89, 134–137]

RNA, Ribonucleic Acid; ACE, Angiotensin Converting Enzyme; TNF, Tumor Necrosis Factor; IL, Interleukin; IMP, Importin.

Table 2: COVID-19 candidate vaccine.

COVID-19 vaccine manufacturer	Vaccine platform	Type	Clinical stage
AstraZeneca	Nonreplicating viral vector	ChAdOx1-S	Phase III
Sinovac	Inactivated	Inactivated	Phase III
Bharat biotech	Inactivated	Whole-virion	Phase III
Moderna	RNA	Lipid nano particle (LNP)-encapsulated mRNA	Phase III
Pfizer	RNA	3 LNP-mRNAs	Phase III
Sinopharm	Inactivated	Inactivated	Phase III
Curevac	RNA	mRNA	Phase III
Anhui Zhifei	Protein subunit	Adjuvanted	Phase II
Vaxart	Nonreplicating viral vector	Ad5 adjuvanted oral vaccine platform	Phase I

[144, 145], FFP3 masks, gowns, eye protection, gloves, and gowns [146–150].

Conclusion

The Covid-19 pandemic has spread all over the globe at an unprecedented pace leaving disaster in its wake. The Covid-19 pandemic presents an immense challenge globally that has been met with a remarkable response through the rapid production of pharmacological research and clinical trials. The most medically advanced countries of the world have buckled under the strain caused due by the rapid spreading of the virus glaring holes in the medical capacity of governments have been exposed such as an insufficient number of hospital beds, inadequate personal protective equipment (PPE) supply, meager morgue capacity, etc. Based on comparison with SARS or MERS the COVID-19 virus has caused more infections and a higher body count. Based on the R_0 values, SARS-CoV-2 is more contagious than SARS or MERS. Immuno-compromised patients and the elderly face a greater risk of fatality compared to the rest of the population. The exact working mechanism of the virus remains a mystery and no drug has been found to completely combat the virus. Therefore, it is imperative to track down the source of infection and cut it down at its origin, cut off the transmission route, and then concentrate efforts in eliminating the virus with the help of available drugs. There is also a need to proactively monitor the progress of the disease. The duration of therapy should be individualized to the patient and the progression of the disease.

At present, management is focused on case detection, monitoring infection, prevention, and supportive care.

Research work, development of new medicines and vaccines, and efforts to reduce disease morbidity and mortality must be encouraged to improve our position in the fight against this disease and to protect human life. Extensive research on therapy, possible vaccines against the virus, and its characterization as a novel virus are a result of the tireless efforts of medical researchers, professionals, academicians, and workers.

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