A Review on COVID-19 and Current Repurposing Treatment Strategy

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Abstract

A recent outbreak was caused by SARS-CoV-2 was named Coronavirus disease- COVID-19. The first case was detected in China. It continued to spread globally and later was declared as a pandemic by WHO. Pneumonia like symptoms was observed which later led to respiratory illness, renal impairment, and death. Closed contact, respiratory droplets through cough, and sneeze are the mode transmission. Symptoms generally occur 2-14 days after infection. PCR is performed using various samples collected from infected patients and is the standard method of diagnosis. Chest X-ray, CT, and the symptoms observed generally show the extent of progress of the disease. Although there is no effective cure, currently symptomatic treatment and supportive care are available to reduce pneumonia-like symptoms and to decrease the severity of the condition. Preventive measures proposed by the WHO is to maintain proper personal hygiene, social distancing, and the use of the mask.

Keywords: *SARS-Cov-2, RNA virus, Symptoms of Covid, Respiratory illness, Treatment strategy, Repurposing.*

Introduction

Numerous cases of pneumonia were detected in Wuhan city, Hubei province, China, and reported to the WHO on 31 December 2019. By the end of the year, cases were reported in all continents to expect Antarctica. The factors that determine the cumulative incidence variation by states were possible, population density, demographics, migration, the extent of testing and reporting, mitigation strategies, etc. The main clinical complication was found to be respiratory illness and renal failure. The causative agent for the pandemic Coronavirus disease (COVID-19) is found to be the newly discovered strains of the Coronavirus.[1]

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History

The history of the human coronavirus traces back to 1965, a virus named B814 was discovered by Tyrrell and Bynoe. Parallelly Hamre and Procknow succeeded in growing a virus with an unusual property named 229E.McIntosh et al while working in the laboratory found multiple strains of organ culture(OC- ether sensitive agents) virus. The three decades that followed encountered large exclusive studies related to human strains OC43 and 229E. There was an outbreak during 2002-2003, namely the SARS infection.

Infections were reported in 29 countries. It accounted for 8098 individuals with 774 SARS – related fatality. The entry of the virus in the human population was then unclear. In 2012, Saudi Arabia identified the first case MERS- CoV. The recent outbreak with unexplained LRTI was seen in the largest metropolitan area, Wuhan in China. The cases were first classified as "pneumonia of unknown etiology". The CDC of China organized an investigation program. The results suggested that the

etiology attributed to the coronavirus (CoV) family. The WHO, on February 11th, 2020 announced the disease as "COVID 19" (acronym of coronavirus disease 2019).[2]

Objective:

The main objective of the article was to review the available information regarding COVID 19 virus. It also explains its origination, the epidemiology, pathophysiology of the disease, methods of diagnosis, existing treatment options, and the prognosis of the disease.

Epidemiology:

It was found that the coronavirus infection occurred more often in a temperate climate. The pediatric and the geriatric population are more prone to infection by the coronavirus. These viruses present in the healthy carriers are accounted to be responsible for 5% to 10 % of acute respiratory infections. To date, the cases are found to be in 215 countries. Today the number of ofCOVID-19 cases is estimated to 20, 824, 419. And the number of recovered cases is 13, 721, 180. The mortality has arisen to a rate of 7, 47, 503.[1]

MORPHOLOGY AND STRUCTURE OF CORONA VIRUS:

Coronaviruses are single-stranded RNA viruses (60-140 nm in diameter), with spike-like projection on the surface, enveloped with projecting glycoprotein that surrounds a core consisting of a matrix protein within a single strand of positive-sense. The glycoprotein present in the envelope plays a crucial role in the attachment to the host cell and transport of the major antigenic epitopes. They were identified as transmissible spherical, pleomorphous particles 132 nm in diameter.[1]

GENOMIC STRUCTURE:

Single-stranded RNA organization approximately 30 kb in length. These RNA viruses are the largest ever known. They have a 5' – cap structure and 3'- poly-A tail.[1]

ETIOLOGY:

- FAMILY- *Coronaviridae*[4]
- SUBFAMILY- *Orthocoronavirinae*[4]
- GENERA- Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), Gammacoronavirus (gammaCoV)[4]

BetaCoV genus is further divided into five subgenera or lineages. Genomic characterization suggests that possibly bat and rodents are the sources of the gene of alphaCoVs and betaCoVs. Contradictory to this, the deltaCoVs and gammaCoVs seem to have their gene sources from avian species. The family of coronavirus is found to cause respiratory, enteric, hepatic, and neurological disease and is found to affect camels, bats, cattle, cats, and humans. Infection in humans is caused by seven human CoVs.[4]

TRANSMISSION:

Analysis of the cases and their spread suggested that close contact (6 feet or 1.8 meters) between individuals is essential for transmission. Statistical data suggests that 80% of the COVID-19 transmissions are asymptomatic in individuals. Studies show that the coronavirus can contaminate surfaces like plastic (virus stays up to 3 days), stainless steel (2-3days), cardboard (24 hours), copper (up to 4 hours). In the first investigation conducted by the Chinese CDC indicated that symptoms would be observed within 12.5 days. On average the incubation period is 2-14 days and the patient infected with the virus begins to show symptoms from the 14th days.

PATHOGENESIS OF SARS-CoV-2 INDUCED PNEUMONIA:

The data available indicates that an excessive immune reaction is produced by the host due to the viral infection. Sometimes the whole reaction that takes place is named "cytokine storm". The condition ultimately results in extensive tissue damage with dysfunctional coagulation. Recently Italian research insinuated the term MicroCLOTS (microvascular COVID-19 lung

vessels obstructive thrombo inflammatory syndrome) concerning viral injury in lungs associated with microvascular pulmonary thrombosis and inflammation. The protagonist of the cytokine storm is Interleukin 6 (IL-6). Also, other cytokines like Tumor Necrosis Factor α (TNF- α), IL-1β, IL-8, IL-12, Interferon-gamma inducible protein (IP10), Macrophage inflammatory protein 1A (MIP 1A), and Monocyte chemoattractant protein phase 1 (MCP 1) are implicated in pathogenic cascade. Activated leukocytes produce IL-6 and exhibit its action on a large number of cells and tissues. IL-6 has pro-inflammatory properties and also anti-inflammatory effects.

CLINICAL FEATURES:

Common symptoms:

Fever, Dry cough, Tiredness, Ache and pain, Sore throat, Diarrhea, Emesis, Conjunctivitis, Headache, Loss of taste or smell, A rash on the skin, or discoloration of fingers or toes – COVID toes.[1,2]

Serious symptoms:

Dyspnea, Chest pain or pressure, Loss of speech or movements.

COMPLICATION:

ARDS, Acute heart injury, Secondary infection, Neurological manifestation, Ocular surface infection, Arrhythmia, Impaired renal function, Abnormal liver functions.

DIAGNOSIS:

Cases may be symptomatic or asymptomatic. A suspected case is confirmed with a positive molecular test. Samples of an oropharyngeal swab, nasopharyngeal swab, sputum, endotracheal aspirates, bronchoalveolar lavage are collected and specific molecular tests are performed on them. Detection of virus can also be present in stool and blood in extremely severe cases.

Laboratory observation:

Usually, low WBC count is observed. Lymphopenia (lymphocyte<1000) is linked to the severe diseased condition. Platelet count is normal or depressed in some cases. Elevation in C-Reactive protein and ESR is observed. However, procalcitonin levels remain normal. Elevation in the procalcitonin level indicates CoV-infection. Severe conditions lead to an elevation in Alanine aminotransferase / Aspartate aminotransferase, prothrombin time, serum creatinine, D-dimer, creatinine Phosphokinase, and lactic acid dehydrogenase is noted.

Chest X-ray:

Show bilateral infiltrates which may be normal in the initial stage.

Computed tomography (CT):

It is considered highly sensitive and specific. It shows infiltrates, ground-glass opacities, and subsegmental consolidation.

Nucleic acid reverse transcription-polymerase chain reaction (PCR):

Currently, PCR is adopted to be the standard method of diagnosis for SARS-CoV-2 infection although there are limitations to the accessibility and availability of PCR test kits.

Serological tests:

Qualitative detection of the virus is based on the presence of IgM / IgG antibody. These tests comprise of ELISA technique, rapid chromatographic tests, and other similar tests. IgM antibodies are seen within 7 days of initial infection. The IgG antibody is found after 14 days of infection.

TREATMENT:

There are no specific vaccines or treatments are available for COVID-19. Clinical trials are being conducted for evaluating potential treatments. Currently, there are treatments to relieve the patient from symptoms and to prevent severity.

Repurposed or off- label drug:

Hydroxychloroquine:

DOSE**:** 400 mg BD on day 1 followed by 400mg daily for the next 4 days.[1]

Drugs currently in use

1.DRUG NAME: CHLOROQUINE/ HYDROXYCHLOROQUINE

CATEGORY: Anti-malarial

MOA IN COVID-19: The drug changes the Ph of endosomes and prevents viral entry and transport

2.DRUG NAME: FAVIPIRAVIR

CATEGORY: Anti-viral

MOA IN COVID-19: the drug inhibits the RNA-dependent RNA polymerase of RNA virus

3.DRUG NAME: INTERFERON BETA

CATEGORY: Immuno-modulator

MOA IN COVID-19: The drug decreases the viral load

4.DRUG NAME: LOPINAVIR/RITONAVIR

CATEGORY: Protease inhibitors

MOA IN COVID-19: blocks viral cellular entry by inhibiting protease

5.DRUG NAME: REMDESIVIR

CATEGORY: Adenosine nucleotide analogs

MOA IN COVID-19: inhibits viral application

6.DRUG NAME: RIBAVIRIN

CATEGORY: Antiviral

MOA IN COVID-19: inhibits viral RNA synthesis and mRNA capping

7.DRUG NAME: GALIDESIVIR

CATEGORY: adenosine analog

MOA IN COVID-19: disruption of viral RNA polymerase

8.DRUG NAME: TOCLIZUMAB

CATEGORY: Monoclonal antibody

MOA IN COVID-19: The drug decreases the pneumonia-like symptoms such as ARDS/ALI

Drugs under trial

1.DRUGS NAME: BEVACIZUMAB

CATEGORY: Monoclonal antibodies

MOA IN COVID-19: The drug prevents from ALI/ ARDS in COVID-19 through suppression of pulmonary edema.

PHASE OF CLINICAL TRIAL: Phase 3

2.DRUGS NAME: INTRAVENOUS VITAMIN C

CATEGORY: Ascorbic acid

MOA IN COVID-19: When sepsis happens, the cytokine surge caused by sepsis is activated, and neutrophils in the lungs accumulate in the lungs, destroying alveolar capillaries. Vitamin C can effectively prevent this process.

PHASE OF CLINICAL TRIAL: Phase 2

3.DRUGS NAME: AZITHROMYCIN

CATEGORY: Macrolide antibiotics

MOA IN COVID-19: This drug helps in the treatment of bacterial infection caused by pneumonia which is a serious complication of COVID-19

PHASE OF CLINICAL TRIAL: Phase 2

4.DRUGS NAME: NANOFENRETINIDE

CATEGORY: Retinoid

MOA IN COVID-19: NanoFenretinide shows inhibitory effects on sars-cov-2 virus replication

PHASE OF CLINICAL TRIAL: Phase 1

5.DRUGS NAME: NICLOSAMIDE

CATEGORY: Anti-helminthic

MOA IN COVID-19: Niclosamide inhibits SARS-COV2 replication and abolishes viral antigen synthesis

PHASE OF CLINICAL TRIAL: Phase 2

Stem cells:

Athersys Inc. began a phase II/III clinical trial in the United States that will examine whether the company's stem cell treatment could potentially benefit people with acute respiratory distress syndrome (ARDS). Mesoblast has also developed a potential stem cell treatment for ARDS.[1]

Blood plasma transfer:

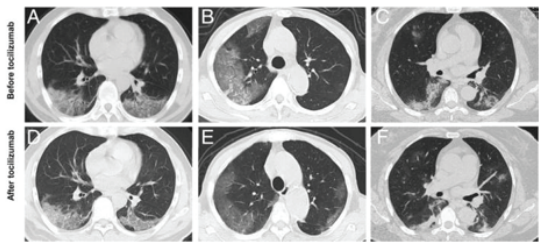
A study on CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and improve clinical outcomes.[2]

Immunosuppressants:

In people infected with COVID 19 large amounts of cytokine is released by overactivity of the Immune system. Several Immuno-suppressants including Baricitinib (usually prescribed for rheumatoid arthritis), CM4620-IE (a drug prescribed for pancreatic cancer) and IL-6 inhibitor are tested under clinical trial to check whether theses drug can curb cytokine storm and minimize the severity of ARDS.[1]

Monoclonal antibody:

Monoclonal antibodies trigger the immune system and attack the virus. Tocilizumab is an antibody that is under clinical trials and is believed to improve the symptoms and repress deterioration of severe COVID-19 conditions.[1]



A-C: Plaque-like and ground-glass opacities before the treatment

D-F: Diffuse infiltration in both lungs, but the lesions were absorbed after the treatment with

Figure 1 Source: Effective treatment of severe COVID-19 patients with tocilizumab, pnas.org

SNG001:

(Synairgen Research's SNG001)

It is an inhalational drug that is tested in clinical trials to treat coronavirus induced conditions like asthma, COPD, and LRTI. SNG001 is a formulation that naturally occurs as Interferon-β. Administered via nebulizer[1].

Ayurveda:

1. AYUSH-64: 02 tablets twice a day.[1]

2. Agasthya Hareetaki: 05 gm twice a day with warm water.[11]

3. Anuthaila/Sesame oil 02 drops in each nostril daily in the morning.[4]

Siddha:

1. Nilavembu Kudineer/Kaba Sura Kudineer—decoction.[14]

Homeopathy:

Various medicine which found to be effective in treating flu-like illness are

1. Arsenicum album[14]
2. Bryonia alba[14]
3. Rhus toxico dendron[14]
4. Belladonna Gelsemium[14]
5. Eupatorium perfoliatum[14]

Vaccines under trials:

1.PLATFORM: Non-Replication Viral Vector

TYPE OF VACCINE: Adenovirus Type 5 Vector

DEVELOPED BY: CanSino Biological Inc./ Beiging Institute of Biotechnology

STAGE OF CLINICAL EVALUATION: Phase 2

2.PLATFORM: RNA

TYPE OF VACCINE: LNP - encapsulated mRNA

DEVELOPED BY: Moderna/NIAID

STAGE OF CLINICAL EVALUATION: Phase 3

3.PLATFORM: Inactivated

TYPE OF VACCINE: Inactivated

DEVELOPED BY: Wuhan Institute of Biological Products/Sinopharm

STAGE OF CLINICAL EVALUATION: Phase 3

4.PLATFORM: Inactivated

TYPE OF VACCINE: Inactivated

DEVELOPED BY: Beijing Institute of Biological Products/Sinopharm

STAGE OF CLINICAL EVALUATION: Early phase 1

5.PLATFORM: Inactivated

TYPE OF VACCINE: Inactivated+ alum

DEVELOPED BY: Sinovac

STAGE OF CLINICAL EVALUATION: phase 3

6.PLATFORM: Non-Replication Viral Vector

TYPE OF VACCINE: ChAdOx1

DEVELOPED BY: University of Oxford

STAGE OF CLINICAL EVALUATION: Early phase 1

7.PLATFORM: RNA

TYPE OF VACCINE: 3 LNP-mRNAs

DEVELOPED BY: BioNTech/Fosun Pharma/Pfizer

STAGE OF CLINICAL EVALUATION: Early phase 1

8.PLATFORM: DNA

TYPE OF VACCINE: DNA plasmid vaccine with electroporation

DEVELOPED BY: Inovio Pharmaceuticals

STAGE OF CLINICAL EVALUATION: Phase 1

9.PLATFORM: Inactivated

TYPE OF VACCINE: Covaxin

DEVELOPED BY: Bharath Biotech; NIV

STAGE OF CLINICAL EVALUATION: Phase 2

PREVENTION:

- Covering mouth and nose with flexed elbow or tissue when coughing or sneezing. Dispose of used tissue immediately. Avoid touching the face.

- Wash hands often with soap and water. Always wear a mask and practice social distancing.
- Take food rich in vitamin C like citrus fruits, vitamin D. Ensure proper hydration.

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Conflict of Interest: Nil

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