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OUTBREAK OF CORONA VIRUS: A DETAILED REVIEW

Syed Muneb Ahmed[1], Mohammed Safi Ur Rahman[2], Syed Abdul Hadi Ghazanfar[3], Govinda Nayak[4], M nirmala[5], S P Srinivas Nayak[6*]

[1](PharmD), Sultan ul uloom College of pharmacy, Hyderabad, Telangana

[2](PharmD), Sultan ul uloom college of pharmacy, Hyderabad, Telangana.

[3](PharmD), Sultan ul uloom College of pharmacy, Hyderabad, Telangana

[4](PharmD), Krishna Teja Pharmacy College, Tirupati, Andrapradesh

[5]Assistant Professor, Krishna Teja Pharmacy College, Tirupati, Andrapradesh

*[6]Assistant professor, Department of Pharmacy Practice, Sultan ul uloom College of pharmacy, Hyderabad, Telangana

Abstract: **The COVID-19 pandemic is spreading across the globe at an alarming rate. Corona Virus is a large family of positive-sense, single-stranded Ribo Nuclic Acid(RNA) viruses that belong to the Nidovirales order. It was first started in Wuhan, Hubei Province, China and then subsequently spread to dozens of other countries becoming a global pandemic. COVID-19 manifests with a wide clinical spectrum ranging from asymptomatic patients to septic shock and multi organ dysfunction. The most common symptoms of patients include fever (98. 6%), fatigue (69.6%), dry cough, and diarrhea. The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, broncho-alveolar lavage or endotrachial aspirate, These samples are then assessed for viral RNA using polymerase chain reaction(PCR). Patients with pre-existing co-morbidities have a higher case fatality rate. These co-morbidities include diabetes (7. 3%), respiratory disease(6.5%), cardiovascular disease(10.5%), hypertension(6%) and malignncy(5.6%). Patients without co-morbidities have a lower case fatality rate(0.9%). Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. No confirmed medication or vaccine has been developed. Current treatment strategies are aimed at symptomatic care and oxygen therapy. Chloroquine phosphate and lopinavir/ritonavir have been suggested. Other suggested anti-virals include ribavirin and abidor. Usage of personal protective equipment, washing hands, sanitization, social distance and general awareness can stop transmission of virus. Prophylactic vaccination is required for the future prevention of COV-related epidemic or pandemic.**

Keywords: **Corona Virus, global pandemic, Wuhan, Hubei Province, China.**

I. INTRODUCTION

Coronavirus(CoV) is a large family of positive-sense, single-stranded RiboNuclicAcid(RNA) viruses that belong to the Nidovirales order. The order includes Roniviridae, Arteriviridae, and Coronaviridae families. The Coronaviridae family is subdivided into Torovirinae and Coronavirinae subfamilies. Coronavirinae is further subclassified into alpha, beta, gamma and deltaCoronavirus[1]. A major difference from common flu virus to Corona virus disease(COVID-19) is that the latter one originates from including common cold to severe syndrome like middle east respiratory(MERS) and severe acute respiratory(SARS). COVID virus is a new strain that is first discovered in humans. It is a zoonosis type of infectious disease that spreads from nonhumans to humans. Even several known corona viruses are circulating in animals that are not yet infected to humans(2).In the month of December 2019, a novel human coronavirus outbreak started in Wuhan, Hubei Province, China and then subsequently spread to dozens of other countries becoming a global pandemic[3].On January 22, 2020, novel CoV has been declared tobe originated from wild bats and belonged to Group 2 of beta-

coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus(SARS-CoV). Although COVID-19 and SARS-CoV belong to the same beta coronavirüs subgroup, similarity at genome level is only 70% and the novel group has been found to show genetic differences from SARS-CoV[4]. There are four classifications found in COVID-19: Alpha, Beta, Delta and Gamma Corona viruses, among them, beta Corona virus divides further into five subgenera. In general this virus contains almost 29000 nucleotides encoding for 9860 amino acids from a single strandedRibo Nucleic Acid(RNA). This genomic structure is organized in a positive sense single stranded RNA(+ssRNA) that can serve as a messenger RNA translates in to protein in the host[5]. There are a number of clinical trials ongoing to study the efficacy of older drugs to be repurposed for use against SARS-CoV-2. One such medication includes the anti malarial Chloroquine(CQ) which was recently cited as a potential treatment to shorten SARS-CoV-2 disease course, mitigate inflammatory responses to infection, inhibit the exacerbation of pneumonia, improve lung imaging findings, and promote a virus negative conversion[3,6,7].CoVs are a diverse family of viruses that interact at multiple levels with components of host cells taking this advantage of some of the cellular machineries for replication and proliferation. Various are known about the molecular biology of CoVs but more information is needed to learn. For example, many of the nonstructural and accessory proteins encoded by these viruses remain uncharacterized with no known function, and it will be important to identify mechanisms of action for these proteins as well as defining their role in viral replication and pathogenesis. Developing technology is going to be getting important insight about structure of CoVs protein to define the mechanism of how protein cause disease and understanding the protein-protein and protein RNA interaction will significantly improve our ability to design vaccines. In the meantime, molecular modelling methods provide important solutions to the struggle[8]

Sources and route of transmission of covid-19:

In recent studies, it hasbeen observed that the novel virus causing epidemics coincides with the CoV isolated in bats. Presence of wild animal trade in Huanan Seafoods Market where the first cases appeared, supports this finding[4,9].Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18)[10]. This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3[11].Often, the human-to-human transmission occurs with close contact. The transmission primarily occurs when an infected person sneezes and through the respiratory droplets produced just as the spread of influenza and other respiratory pathogens. These droplets can settle in the mouth or nasal mucosa and lungs of people with inhaled air[12]. Currently, it is clear that a person can be infected by COVID-19 by touching an infected surface or object and then touching their mouth, nose, or possibly eyes.

II. PATHOPHYSIOLOGY

Genome structure of Corona virus:

Coronaviruses encode five structural proteins in their genomes(mentioned in fig.1). These are the Spike(S), Membrane(M), Envelope(E) glycoproteins, Hemagglutinin Esterase(HE) andNucleocapsid(N) protein.All envelope proteins and N protein is present in all virions but HE is only present in some beta coronaviruses[13]. S Glycoproteins are located outside the virion and give the virion the typical shape. The S proteins form homotrimers, which allow the formation of sun-like morphologies that give the name of Coronaviruses [14,15,16].The M protein plays a key role in regenerating virions in the cell. N protein forms a complex by binding to genomic RNA and M protein triggers the formation of interacting virions in this endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) with this complex [17,18,19]. The N proteins are phosphoproteins that are capable of binding to helix and have flexible structure of viral genomic RNA. It plays an important role in virion structure, replication and transcription of coronaviruses, because the N protein localizes in both the replication/ transcriptional region of the coronaviruses and the ERGIC region where the virus is collected [20-28].

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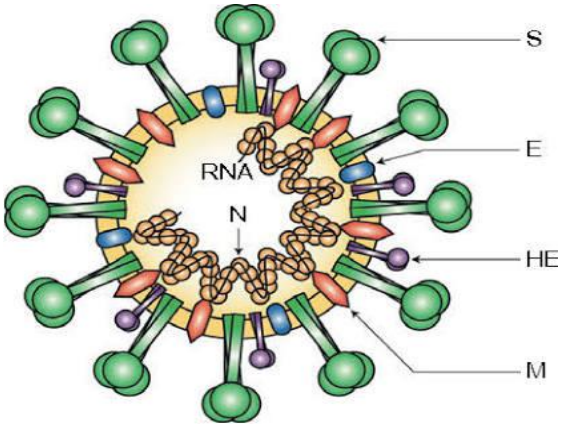

Fig.1: Coronavirusvirion structure shown with structural proteins N: Nucleocapsid protein; S: Spike protein,M: Membranprotein, HE: Hemagglutinin-Esterase andE: Envelope protein [29]

The coronavirus spike contains three segments: a large ectodomain, a single-pass transmembrane anchor and a short intracellular tail. The ectodomain consists of a receptor-binding subunit S1 and a membrane-fusion subunit S2. Electron microscopy studies revealed that the spike is a clove-shaped trimer with three S1 heads and a trimeric S2 stalk[30-33]. During virus entry, S1 binds to a receptor on the host cell surface for viral attachment and S2 fuses the host and viral membranes, allowing viral genomes to enter host cells. Receptor binding and membrane fusion are the initial and critical steps in the coronavirus infection cycle; they also serve as primary targets for human inventions[34]. The life cycle of the virus is deplected in fig.2.

The replication of coronaviruses occurs in host cell cytoplasm. The viruses primarily bind to the receptor on the cell surface via the spike (S) protein. When S protein is bound to the receptor, a conformational structure occurs in the structure and the process of entry into the virus cell begin. This process with endocytosis is dependant of pH through the receptor. After entering the cytoplasm, the virus particle releases the RNA genome. This genome is a single-stranded, non-segmented RNA virus with the largest known RNA genome(gRNA), which is approximately 26-32 kb The genome consists of seven genes. It is organized into 5'non-structural protein coding regions comprising the replicase genes (gene 1), which are two-thirds of the genome, and 3' structural and nonessential accessory protein coding regions comprising the gene 2-7. Thereplicase gene 1 products are encoded two very large open reading frames ORF1a and 1b, which are translated into two large polypeptides pp1a and pp1b, which are synthesized directly from the 5' two-thirds of the genomic RNA of CoV. After synthesis of these proteins, consisting of 16 units, non-structural protein (nsp1to nsp16) is converted with the contribution of viral proteases pp1a and pp1b. These 16 proteins form Double-Membrane Vesicles(DMV). At the same time, this DMV is virus Replication and Transcription Complex (RTC). These nsp proteins, especially non-structural protein3 (nsp3), have an important role in the virion structure, the replication and transcription of CoV.

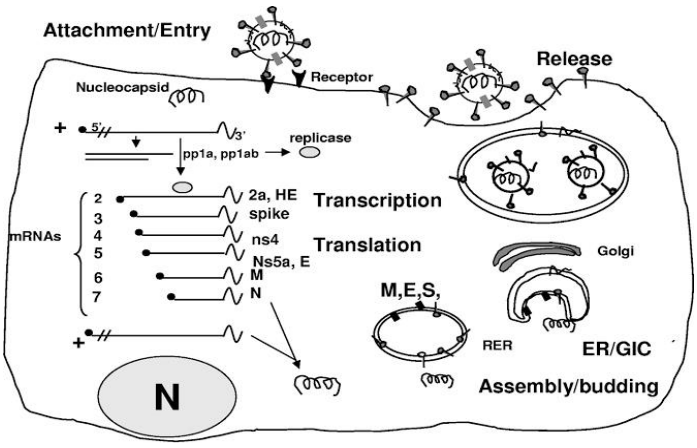

Fig.2: Coronavirus' life cycle [35]

III. CLINICAL FEATURES

COVID-19 manifests with a wide clinical spectrum ranging from asymptomatic patients to septic shock and multiorgan dysfunction[36]. COVID-19 is classified based on the severity of the presentation[36]. The disease may be classified into mild, moderate, severe and critical[38]. The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, anddiarrhea[38]

Patients with mild illness may present with upper respiratorytract viral infection like dry cough, mild fever, nasal congestion, sore throat, head ache, muscle pain and malaise. Among infected cases majority (81)% are mild[36]

Patients with severe disease present withsevere pneumonia. Acute respiratory distress syndrome(ARDS) and septic shock[36]. Clinical presentations include the presence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, SpO2 $\leq$ 93%, PaO2/FiO2 < 300, and/or greater than 50% lung infiltrates within 24 to 48 hours[36]. Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling, and altered mentation[36].

IV. DIAGNOSIS

The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage or endotrachial aspirate,These samples are then assessed for viral RNA using polymerase chain reaction(PCR)[36].The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g.vasculitis and dermatomyositis) common respiratory disorders like Adenovirus, Influenza, Human metapneumovirus(HmPV), Parainfluenza, Respiratory syncytial virus (RSV), Rhinovirus(common cold)For suspected cases, rapid antigen detection and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions[37].In addition to the clinical and ventilatory criteria, chest imaging modalities such as chest X-ray, computed tomography(CT) scan and lung ultrasound can be used to support the diagnosis. Laboratory evidence of other homeostatic dysregulation includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy[36]. Patients with septic shock are persistently hypotensive despite volume resuscitation. They may also have an accompanying serum lactate level of >2 mmol/L.

V. COMPLICATIONS AND FATALITY RATE:

Severe pneumonia, Acute respiratory distress syndrome(ARDS), sepsis or septic shock[36]. Even in severe forms of the disease, fever can be absent or moderate. In addition, 5% of patients can develop a critical disease with features of respiratory failure, RNAaemia, cardiac injury, septic shock or multiple organ dysfunction [36,38]. Data from the Chinese CDC suggest that the case fatality rate for critical patients is 49%[36]. Patients with pre-existing co-morbidities have a higher case fatality rate. These co-morbidities include diabetes (7.3%), respiratory disease(6.5%), cardiovascular disease(10.5%), hypertension(6%) and malignncy(5.6%). Patients without co-morbidities have a lower case fatality rate(0.9%)[38].

VI. PREVENTIVE MEASURES

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with patients, farm animals, and wildPrevention[36].The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.

➢ Individuals who areimmuno-compromised, co-morbid conditions, using corticosteroids and organ transplanted should avoid public gatherings[37]

VII. MANAGEMENT

Isolation remains the most effective measure for containment of COVID-19. No specific antiviral medication or vaccine is currently available[36]. Therefore, the treatment of COVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements and sometimes anti-bacterial therapy[38]. Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation(ECMO), glucocorticoid therapy and convalescent plasma[38]. The administration of systemic corticosteroids is not recommended to treat Acute respirato distress Syndrome[38].Therapeutically, aerosol administration of alpha-interferon(5 million units twicedaily), chloroquine phosphate and lopinavir/ritonavir have been suggested[36]. Other suggested anti-viralsinclude ribavirin and abidor.Preclinical studies suggested that remdesivir(GS5734)an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola could be effective for both prophylaxis and therapy of corona infections.[39].Treatment of septic shock requires hemodynamic support with theadministration of vasopressors. Organ function support is necessary for patients with multiple organ dysfunction [36]

VIII. COUNCELLING POINTS TO THE PATIENT,CARE GIVER AND GENERAL PUBLIC

➢ Emergency medicine departments must apply strict hygiene measures for the control of infections. Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, gowns, eye protection, gloves, and gowns.

➢ The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow)

➢ Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water.

➢ Maintain at least 1 metre (3 feet) distance between yourself and anyone who is coughing or sneezing. When someone coughs or sneezes they spray small liquid droplets from their nose or mouth which may contain virus. If you are too close, you can breathe in the droplets, including the COVID-19 virus if the person coughing has the disease and you may be infected.

➢ Avoid touching eyes, nose and mouth because Hands touch many surfaces and can pick up viruses. Once contaminated, hands can transfer the virus to your eyes, nose or mouth. From there, the virus can enter your body and can make you sick.

➢ Practice respiratory hygiene, Make sure you, and the people around you, follow good respiratory hygiene. This means covering your mouth and nose with your bent elbow or tissue when you cough or sneeze. Then dispose of the used tissue immediately.

➢ Stay home if you feel unwell. If you have a fever, cough and difficulty breathing, seek medical attention and call in advance. Follow the directions of your local health authority. National and local authorities will have the most up to date information on the situation in your area. Calling in advance will allow your health care provider to quickly direct you to the right health facility. This will also protect you and help prevent spread of viruses and other infections.

➢ Stay informed on the latest developments about COVID-19. Follow advice given by your healthcare provider, your national and local public health authority or your employer on how to protect yourself and others from COVID-19. National and local authorities will have the most up to date information on whether COVID-19 is spreading in your area. They are best placed to advise on what people in your area should be doing to protect themselves.

➢ Stay at home if you begin to feel unwell, even with mild symptoms such as headache and slight runny nose, until you recover. Avoiding contact with others and visits to medical facilities will allow these facilities to operate more effectively and help protect you and others from possible COVID-19 and other viruses.

➢ If you develop fever, cough and difficulty breathing, seek medical advice promptly as this may be due to a respiratory infection or other serious condition. Call in advance and tell your provider of any recent travel or contact with travelers. Calling in advance will allow your health care provider to quickly direct you to the right health facility. This will also help to prevent the spread of virus[40]

IX. CONCLUSION

The COVID-19 pandemic is spreading across the globe at an alarming rate CoV is a large family of positive-sense, single-stranded RiboNuclic Acid(RNA) viruses that belong to the Nidovirales order. It was first started in Wuhan, Hubei Province, China and then subsequently spread to dozens of other countries becoming a global pandemic.It has caused moreinfections and deaths as compared with SARS or MERS. Elderly and immunocompromised patientsare at the greatest risk of fatality. The rapid spread of disease warrants intense surveillance andisolation protocols to prevent further transmission. No confirmed medication or vaccine hasbeen developed. Current treatment strategies are aimed at symptomatic care and oxygen therapy chloroquine phosphate and lopinavir/ritonavir have been suggested. Other suggested anti-virals include ribavirin and abidor. Usage of personal protective equipment, washing hands, sanitization, social distance and general awareness can stop transmission of virus. Prophylactic vaccination is required for the future prevention of COV-related epidemic or pandemic.

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