



COVID-19-A NEW CHALLENGES FOR PREVENTION AND THERAPY

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Abstract:

In December 2019, a novel coronavirus named as SARS-CoV-2 caused a sequence of acute atypical respiratory diseases. The virus initiated in bats and was transferred to humans through yet unknown intermediate animals in Wuhan, Hubei Province, China 2019. The disease caused by this virus was named COVID-19. The symptoms related with this illness are cough, fever, running nose, mostly the respiratory issues. The peculiar thing is there is no accessible treatment or vaccine to treat this disease. There are only protective measures that can stop or control this virus spread. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic, including the U.S. Centers for Disease Control and Prevention (CDC) are monitoring the pandemic and posting updates on their websites. WHO launched the "Solidarity" is an international clinical trial to help find an effective treatment for COVID-19. Clinical trials and investigations to find out more about the virus, its origin, how it affects humans, and its management are ongoing. Several antiviral agents have been explored as possible therapeutic options to address the COVID-19 pandemic. Epidemiological studies showed that older patients were more vulnerable to severe diseases, however childrens tend to possess milder symptoms. Here we reviewed the updated knowledge about this syndrome and measured the possible description of the different symptomatology among childrens and adults. There have been nearby 96,000 described cases of corona virus disease 2019 (COVID-19) and 3300 described deaths to date (05/03/2020).

Keywords:

Covid19, Pandemic, Pneumonia, SARS Cov-2, Outbreak response management, WHO

Introduction:

Coronaviruses are a family of viruses which will cause illnesses like the cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In December 2019, a new coronavirus was identified, a sequence of severe atypical respiratory disease occurred in Wuhan, china. ^(7,8) This rapidly spreads from Wuhan to further areas. It was soon discovered that a novel coronavirus was responsible. The novel coronavirus was named as the severe acute respiratory syndrome coronavirus-2 (sars-cov-2, 2019ncov) due to its high homology (~80%). Most people with covid-19 have minor to reasonable symptoms like tired, cough, fever, shortness of breath or difficulty of breathing, chills, muscle aches, headache, sore throat, loss of taste or smell, pain . The disease can cause severe therapeutic difficulties and cause death in a number of people. Older adults or people with existing chronic remedial conditions are at superior risk of becoming completely ill through covid-19.^(8,9) In March 2020, the planet Health Organization (WHO) declared the COVID-19 outbreak an epidemic.⁽⁴⁷⁾ On 11 March 2020, the rapid increase in the number of cases outside China led WHO Director-General Dr. Tedros Adhanom Ghebreyesus to announce that the outbreak could be characterized as a pandemic.^(11,12,13) By then more than 118000 cases had been reported in 114 countries, and 4291 expiries had been recorded. In mid-March 2020, the WHO European Region had become the epicenter of the epidemic, reporting above 40% of worldwide definite cases. As of 28 April 2020, 63% of worldwide deaths from the virus were from the Region.⁽¹⁾

Pathophysiology and epidemiology of covid 19 of human:

Statistics from the biggest case series in China found that 3% definite cases were aged 80 years and 87% of definite cases were aged 30 to 79 years or older. Approximately 49% of patients were female and 51% were male. Nearly 4% of cases were in healthcare workers, with 23 deaths described. Timely records from a small retroactive study in Italy found the middle age and the prevalence of comorbidities to be greater in this population equated with the studies from China.⁽¹⁰⁾ In the US, older patients (aged ≥ 65 years) accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths, with the maximum prevalence of severe consequences in patients aged ≥ 85 years. In the UK, the median age of patients admitted to hospital in a small cohort of 95 patients was 75 years, and males accounted for 63% of admissions.^(52,29)

Children are less affected than adults. Children account for only 1% to 5% of definite cases. Only 2.1% of reported cases in a big case series in China were aged 0 to 19^(4,5). The middle age of infected children in China is 7 years. Data from the UK indicate that the prevalence of infection is less than 5% in patients younger than 18 years of age, with a higher risk in males. In the US, children accounted for only 1.7% of all cases. The median age of infected children and young adults in a hospital in Washington, DC, was 9.6 years; the median age in non-hospitalized patients was similar. However, the median age was significantly higher in critically ill patients.^(53,22)

In India more than 5600 cases saw in a per day at the 21 may 2020.Total confirmed cases of covid 19 were 106750, even nearly 40% of the overall patients were cured. There are 61149 active cases in India , of which 6.9% require oxygen, ventilator support or intensive care unit treatment .⁽¹⁶⁾

Pathophysiology:

SARS-CoV-2 may be a virus belongs to a family of single-stranded RNA viruses referred to as coronaviridae, may be a common sort of virus In humans, it commonly causes mild infections, associated with the cold and 10–30% of upper tract infections in adults, it can cause enteric and nervous disorder .The time period of a coronavirus is usually up to 2 weeks. SARS-CoV-2 may be a new strain of coronavirus, although the time period of this strain is currently unknown, the U.S Centers for Disease Control and Prevention designate that symptoms could seem in minimum 2 days maximum 14 days after exposure. Originated during a foodstuff in Wuhan and consequently spread from animal to human. Any research has claimed that the cross-species transmission could also be among snake and human.⁽¹⁶⁾ As this coronavirus affects the tract , commonly giving symptoms include dry cough and fever, with some respiratory symptoms (e.g. pharyngitis, nasal congestion, malaise, headache and myalgia) or maybe struggling for breath.^(38,39)

Coronavirus spread through droplet by an ill person to strong person as person touches facial skin virus enters through mucus and an attack on the lungs. Alveoli which are present in lungs, which functioning as a transfer of O₂ and CO₂. Alveolar cells surfactants of alveoli, which supports in protecting the alveoli and permit to transmission of the O₂ and CO₂, coronavirus attaches to those cells with the assistance of receptor ACE2. Afterwards the entry into cell endocytosis is occurring which releases genome of viruses. Genome containing Single standard RNA(ssRNA) attaches to ribosomes present in cell and begin replicating into negative single standard RNA (ssRNA) and over into positive ssRNA which replicate as small ssRNA.⁽⁴²⁾ While viruses self-replicating in alveolus cell it also damages this may initiate primary inflammatory response, damage alveolar cell releases interferon cytokinins and intra cellular components.

Interferon acts in paracrine manner, preparing them to keep off the infection the first function is to induce protection against viruses in neighboring non infected cells. Alveolar macrophages distinguish cell injury via damaged allied molecular forms from alveolar cells. They also respond to released cytokine from injured alveolar cells and macrophages secretes cytokine like TNF alpha, interleukin1, interleukin6, interleukin 8 and other chemokine. The inflammatory response occurring in lung parenchyma stimulate nerve end liable for cough reflex and dry cough first indication of Covid-19 we observe.^(1,2)

Due to interleukin and chemokine neutrophils and monocytes attract they increase in vascular permeability causes leakage of the fluids into the interstitium causing intestinal edema and into the alveoli causing pulmonary edema and this may cause dyspnea and impaired oxygenation resulting in hypoxemia. The rise in leukocyte count in serum means increasing in circulating macrophages and neutrophils, while neutrophils are important within the acute setting by engulfing viruses. Because it releases chemicals by-product damaging the encompassing tissue, and get damaged alveolus cell alveolar and this suggests less surfactant being productive, which is definitely collapse these alveoli this may end in reduced oxygenation leading hypoxemia. The White blood corpuscle and damaged endothelial cell releases arachnidonic acid metabolites

including leukotrienes and prostaglandin leukotrienes will cause bronchoconstriction resulting in the hypoxemia.⁽⁶⁾

Prostaglandins interleukin 1, interleukin 6 and TNF ALPHA all liable for causing fever, Decreased oxygen level in blood will stimulate chemo receptor within the aorta and within the brain, which stimulated chemo receptors will then stimulate the cardiopulmonary centers within the brain to inform the lungs breathe more so as to extend oxygen levels in the blood and heart to pump faster to deliver oxygen to the body which is why patients who have hypoxemia are usually tachypnea also as tachycardia. Injured lung, accumulation of fluid, ventilation/perfusion mismatch and hypoxemia that's not associated with heart function is what's called ACUTE RESPIRATORY SYNDROME and is that the leading explanation for the mortality within the Covid-19.⁽³⁷⁾

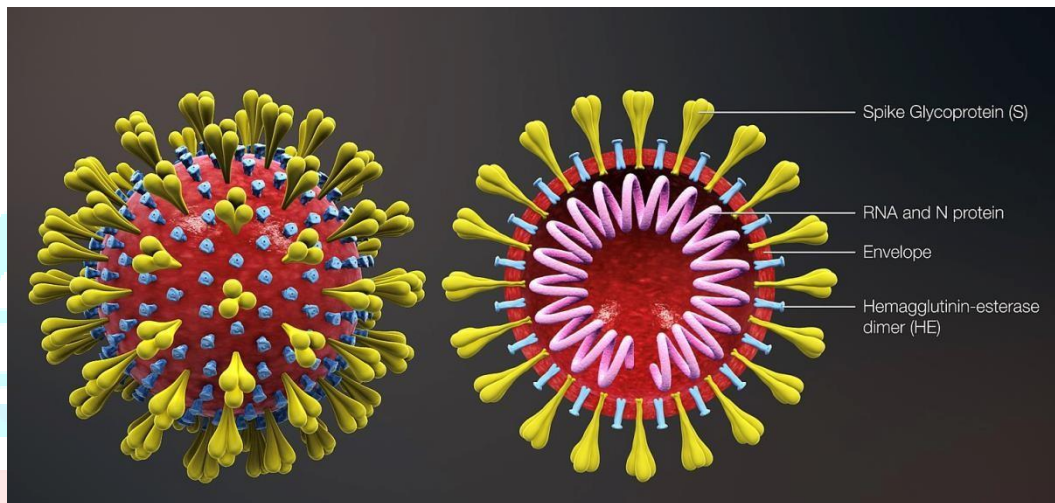


Fig1: - Structure of COVID-19

How does covid-19 appear in human?

Coronaviruses are zoonotic. This means they firstly developed in animals previously developing in humans. The 2019 coronavirus hasn't been completely connected to a specific animal. Researchers have confidence in that the infection may have been conveyed from bats to another animal either snakes or pangolins and afterward the infection transmitted to humans. The virus pass from animal to humans if a person has individually come into close contact with an animal that conveys the disease. This transmission happened in the open food market in Wuhan, China.^(41,42)

Once the virus develops in individuals, coronaviruses can be transmitted from individual to individual through respiratory beads by coughing or sneezing. Doctors or specialists are learning new things about this virus consistently. Up until now, we realize that COVID-19 may not at first reason any side effect for certain people however few people groups develop side effects. Normal indications of disease incorporate respiratory side effect, fever, hack, shortness of breath and breathing difficulties. The most genuine confusions of COVID-19 In progressively serious cases, disease can cause pneumonia, extreme intense respiratory disordered, kidney disappointment and even death.⁽³⁾

Youngsters make up a little extent of reported cases; with about 1% of cases being under 10 years and 4% matured 10–19 years. They have milder side effects and a lower possibility of extreme infection than grown ups; in those youthful than 50 years the danger of death is under 0.5%, while in those older than 70 it is over 8%. Pregnant ladies may likewise be higher danger of serious contamination with COVID 19. In China, kids acquired disease, mostly through close contact with their folks or other relatives.^(14,15)

Preventive measures of covid 19:

To reduce the chances of infection include:

1. Wash hands frequently with cleanser and water for at any rate 20 seconds or a liquor based hand sanitizer (that contains at any rate 60% liquor), particularly in the wake of being in an open spot, cleaning out their nose, or hacking/sneezing.⁽³⁴⁾
2. Avoid contacting the eyes, nose, and mouth without washing hands.
3. Avoid close contact with individuals (i.e., keep up a separation of at any rate 1 meter [3 feet]) with shaking hands, especially the individuals who are wiped out, have a fever, or are hacking or wheezing. The U.S. Habitats for Sickness Control and Anticipation (CDC) suggests covering the mouth and nose with a tissue when hacking or wheezing and utilizing within the elbow if no tissue is accessible.
4. It is essential to take note of that suggested separations contrast between nations (for instance, 2 meters is suggested in the US and UK) and you ought to counsel nearby direction.
5. Avoid going to swarmed places.
6. Practice respiratory cleanliness (i.e., spread mouth and nose when hacking or wheezing, dispose of tissue promptly in a shut canister, and wash hands).
7. Seek clinical consideration early on the off chance that they have a fever, hack, and trouble breathing, and offer their past movement and contact history (voyagers or suspected/affirmed cases) with their human services supplier.

PREVENTION CORONAVIRUS



Fig2: - Prevention to coronavirus⁽³⁴⁾

8. Stay at home and self-detach on the off chance that they are wiped out, even with gentle side effects, until they recuperate (but to get clinical consideration).
9. Clean and sterilize as often as possible contacted surfaces day by day (e.g., light switches, door handles, ledges, handles, telephones) as per nearby social propensities. Counsel nearby direction for more data.
10. The World Wellbeing Association (WHO) suggests that clinical covers ought to be saved for medicinal services laborers. Individuals with manifestations ought to likewise wear a clinical cover, self-segregate, and look for clinical guidance at the earliest opportunity. Covers are likewise suggested for those thinking about a wiped out individual at home when in the equivalent room.^(17,23)

Treatment of covid-19:

According to World Health Organization there's no definite treatment for COVID 19. They gave us Emergency Use Approval (not full approval) for remdesivir in individuals hospitalized with serious COVID 19 after an investigation proposed it decreased the duration of recuperation. The researchers are endeavouring to create successful treatments.⁽²⁷⁾

The WHO and NIH don't restrict the usage of non-steroidal anti-inflammatory drugs (NSAIDs) suggested by some clinical experts like ibuprofen and paracetamol for indications and subsequently the FDA says at present there's no proof that NSAIDs compound COVID 19 side effects. Treatments that are under assessment incorporate medications that are wont to treat malaria and autoimmune diseases; antiviral

medications that were created for different infections, and antibodies from one that have recovered from COVID-19. In cases where the individual's life is genuinely or quickly threatened the convalescent plasma as an experimental treatment used granted by FDA. It's sheltered and compelling for the disease.⁽⁴⁵⁾

Convalescent plasma:

At the point when individuals get over COVID-19, their blood contains antibodies that their bodies delivered to fight against coronavirus. Antibodies are a component of blood found in plasma. Literally convalescent plasma has been utilized for quite 100 years to treat a spread of illnesses from measles to polio, chickenpox, and SARS. Inside the ebb and flow circumstances, neutralizer containing plasma from a recuperated patient is given by transfusion to a patient who is influenced by COVID-19.⁽⁴⁶⁾ These antibodies help the patient battle against illness, possibly reducing the seriousness of the ailment and improving the health of the patient.

Though convalescent plasma has been used for several years, and with varying success, not much is understood about how effective it's for treating COVID-19.⁽³¹⁾ Experts also don't yet know the simplest time during the course of the illness to offer plasma. There are reports of success from China, but no randomized, controlled studies are done. On March 24th, the FDA started permitting healing plasma to be utilized as an trial treatment in patients with genuine or promptly life-threatening COVID-19 contamination. So as to give plasma, an individual must meet few rules. They need to possess established positive for COVID-19, recovered, haven't any indications for 14 days, currently test negative for COVID-19, and have high enough antibody levels in their plasma. A donor and patient must even have compatible blood types. Once the plasma is donated, it's screened for other infectious diseases, like HIV.^(32,33) Each donor produces enough plasma to treat one to 3 patients.

Antiviral treatment:

Currently there's no definite antiviral treatment for COVID-19. However, previously developed drugs to treat other viral contaminations are being established to ascertain if they could even be effective against the virus that causes COVID-19.

Remdesivir:

Remdesivir was developed to treat several other severe viral diseases, including the disease caused by the Ebola virus. Coronavirus that causes COVID-19 is analogous to the coronaviruses that caused the diseases SARS and MERS — and suggestion from laboratory and animal studies suggests that remdesivir may help limit the reproduction of the virus and spread the viruses within the body.^(22,23) It works by inhibiting the power of the coronavirus to breed and make copies of itself: if it can't reproduce, it can't make copies that spread and infect other cells and other parts of the body.⁽²⁸⁾

The drug was effective in treating the coronaviruses in animals: there was a discount within the amount of virus within the body, and also an improvement in lung disease caused by the virus. Remdesivir was utilized

in the primary case of COVID-19 that occurred in Washington state, in January 2020. The patient was severely ill, but survived. Of course, experience in one patient doesn't prove the drug is effective.^(43,46)

National Institutes of Health (NIH) strategies mentioned remdesivir for the treatment of COVID-19 in hospitalized patients with serious illness necessitating supplementary oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. The rules panel doesn't recommend remdesivir for the treatment of mild or moderate COVID-19 outside the setting of a clinical test . The drug is being tested in many COVID19 clinical trials round the world.

In the trial, evaluating 5-day and 10- day dosing, duration of the drug remdesivir in coronavirus patients . The effectiveness of the drug was measured in terms of medical development described in patients starting from development in breathing, increased level of oxygen support to hospital discharge. Nearly 50% Of patients within the 5-day treatment showed clinical improvement in 10-days quite half patients in two treatment groups of the clinical test were discharged from the hospital by day 14. The trial was conducted by Gilead Sciences, Inc.^(35,36)

Kaletra:

An oral antiretroviral PI is a mixture of two drugs - lopinavir and ritonavir - that employment against HIV, has been utilized in clinical trials for the treatment of COVID-19. Most viruses have the power to make proteins necessary for his or her life cycle. The lopinavir and ritonavir combination stops that process. For viruses make their DNA or RNA (RNA within the case of SARS-nCov-2) the virus has got to take hold of a number of the proteins within the host cell.⁽⁴⁶⁾

A lot of the involvement with lopinavir and ritonavir, like all the medicines the medical profession is annoying beside the coronavirus pandemic, is drawn from the practise with the SARS outbreak in 2003. It had been an option, but not clearly operative against the virus, consistent with trials done at the time.⁽⁴⁰⁾ As of this article's publication date of April 7, 2020, the foremost current education on lopinavir and ritonavir was published March 2020 within the New England Journal of drugs where they compared lopinavir and ritonavir with the present standard of care (compassionate care to alleviate indications with no antiviral medication).^(30,27)

Cao et al. Administered a randomized, controlled, open-label trial, for lopinavir–ritonavir (ritonavir helps to stabilize lopinavir) in 199 hospitalized patients with severe COVID-19, of whom 99 were assigned to the treatment group, and 100 received the quality of care. The authors found no advantage of lopinavir–ritonavir time to clinical improvement beyond the quality of care, although lopinavir–ritonavir was found to possess benefit of a few secondary endpoints, the security of the treatment was confirmed.⁽¹⁹⁾

Chloroquine or Hydroxychloroquine and Azithromycin

Hydroxychloroquine and chloroquine are primarily want to treat malaria and a number of other inflammatory diseases, including lupus and atrophic arthritis . Reports from China and France suggested that patients with severe symptoms of COVID-19 improved more quickly when given chloroquine or hydroxychloroquine.^(25,26) Some doctors were employing a combination of hydroxychloroquine and azithromycin with some positive effects. Azithromycin may be a commonly prescribed antibiotic for streptococcal sore throat and bacterial pneumonia. Hydroxychloroquine and chloroquine are shown to kill the COVID-19 virus within the laboratory dish.^(24,25) Both medications are related to QTc prolongation which increases the danger of drug induced Torsade's de pointes and sudden cardiac death. The 2 sort of mechanisms of those drugs appear. First, they create it tougher for the virus to connect itself to the cell, preventing the virus from incoming the cell and reproducing within it. Second, if the virus does achieve to urge exclusive the cell, the drugs destroy it before it can reproduce. Azithromycin isn't used for viral contaminations. However, this antibiotic does have some anti-inflammatory action.^(50,51) There has been assumed, yet not ever proven, that azithromycin may beneficial to diminish an overactive immune reaction to the COVID-19 infection. Chloroquine or hydroxychloroquine alongside macrolides is widespread to supply accurate clinical guidance often with slight regard for possible risk. The aim of this study was to gauge the utilization of chloroquine or hydroxychloroquine only or together with an Azithromycin for treatment of COVID-19 employing a large multinational registry to assess their real-world application.^(18,19)

NSAIDs:

Non-steroidal-an inflammatory drugs are most ordinarily used and have a good range of uses. It includes an"art-24">The WHO initially recommended using acetaminophen rather than ibuprofen to assist reduce fever and aches and pains associated with this coronavirus infection. If you think or know you've got COVID-19 and can't take acetaminophen, or have taken the utmost dose and still need symptom relief, taking over-the-counter ibuprofen doesn't get to be specifically avoided.⁽⁵¹⁾

Mechanical ventilation:

This course will afford licensed medical specialised with an understanding of mechanical ventilation so as that they will contribution with the operation of mechanical ventilators during covid19 pandemic. The increasing number of patients contracting COVID-19 and developing pneumonia.⁽⁴³⁾ Ventilators should be used under the supervision of a qualified licensed medical professional. Access the manufacturer's directions for the specific expedient you are using and the product information sheet for any drug administered.⁽³⁶⁾

About 5-15% patients with covid 19 infection require intensive care surveillance and ventilator support. Current recommendations suggest early intubation of covid 19 patients mainly two reasons, i.e. severe hypoxemia and to protect staff from viral transmission . Mortality during mechanical ventilation appears to be high, however lung protective ventilation is mandatory. Many patients of covid 19 occurred pneumonia are initially characterized by relatively well preserved lung compliance despite severe hypoxemia. Pathophysiology of covid 19 i.e. the viral infection may lead to sub pleural inflammation, increase in

vascular permeability and edema. Impaired vasoreactivity with vasoplegia may counteract hypoxic vasoconstriction which easily estimated^(43,44). The physiologic response to hypoxemia is increased ventilation with increased tidal volume and respiratory rate also increased.

Conclusion:

The pandemic by COVID-19 is a live issue affecting people worldwide. Without fundamental therapeutic interventions, current organization is to diminish the virus spread and provide helpful care for diseased patients. There is a crucial need to develop targeted therapies. COVID-19 restrained to the accompanying airlines should be slight and preserved symptomatically at home. However, COVID-19 has developed to the gas exchange units of the lung must be observed prudently and reinforced to the greatest of our capability, as we expect the growth and difficulties of definite antiviral drugs.

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