Review Article

Coronavirus :- An Emerging Pathogen

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Abstract

Corona virus disease -19(COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Primarily it causes respiratory illness in humans. The pandemic caused by ths virus started in 2019 in Wuhan , China. Later it was declared as pandemic by WHO. In this article I am reviewing the coronavirus along with its microbilogical structure, transmission, pathogenesis, clinical features and its management. The virus is a singl stranded RNA virus. The virus enters the respiatory tract via mucous membrane of mouth or nose. It binds to ACE TYPE 2 receptor and causes alveolar edema and its destruction leading to decrease in gas exchange which further leads to hypoxaemia finally leading to acute respiratory distress syndrome (ARDS). It most patients COVID19 presents with mild symptoms and they doesn't require any medical intervention. But patietnts presenting with severe symptoms needs vigilant medical attention and may require ventilatory support. Most common symptoms are fever, dry cough, shortness of breath, fatigue , nasal congestion. The infection spreads via droplet from an infected person. Infection with this virus may lead to severe inflammatory response leading to release of cytoines which causes increased capillary permeability and vasodilatation leading to hypotension which further leads to decrease in blood supply to multiple organs leading to multiple organ failure. There is increase chances of morbidity and mortality among elderly and in those with comorbidities. In eldrely the chance of fatality is way more than young people. No one drug has been found yet as the ultimate treatment of COVID-19. Many drugs are under clinical trial and researches are going on for vaccine as well. But untill we get a definitive cure the only escape we have is prevention and the only means to do that is to practice social distancing , proper hand hygiene and sanitation.

Keywords:- *SARS-CoV2, pathogenesis, transmission, ACE 2 receptor, alveolar edema, ARDS, prevention, Ground glass opacities, hydroxychloroquine, remdesivir.*

Introduction

Coronavirus term is derived from corona that means crown like and this crown like morphology is seen on electron microscopy. This morphology is due to club shaped peplomers arising from the envelop.

Coronavirus is enveloped, single-stranded, positive-strand RNA virus. It is belongs to the order Nidovirales . This coronavirus family constists of pathogens for many animal species including humans . The recent pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).[1]

Coronavirus disease 2019 (COVID-19), is also called as Wuhan-Hu-1-CoV because it has emerged from Wuhan, China in December 2019. At the start of 2020, the causative agent of COVID-19 was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).[1] After the rapid spread of coronavirus in various parts of the world, World Health Organisation (WHO) declared it as PANDEMIC.

During the start of corona virus infection it presents in a similar fashion like common cold and many times patient might be asymptomatic. Theryby they transmit the infection to others unknowingly via droplet spread. People of older age and people with comorbidities are at highr risk of contarcting the infection baecause of their weakened immune system and comorbidities their immune response is compromised which render them more susceptible . Most patients of younger age present with mild symptoms and do not need any as such medical attention foe their recovery , all tey need to do is to self isolate themselver so as to brake the chain of transmission. But at the same time the eldrely need

medical assistance to survive.

CORONAVIRUS LINEAGE:-

ORDER- Nidovirales

FAMILY- coronaviridae

The Coronavirinae and the Torovirinae are the two subfamilies of the family Coronaviridae . The coronavirinae is again divided into four genera: Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus. Coronavirus is widespread and maximum variety of genotypes infect bats . But Alphacoronavirus and Betacoronavirus are subcategories which affects the humans.[1,2,3]

MICROSCOPY:-

Coronavirus is an enveloped virus. It has a large plus-strand RNA genome of size the 27-32 kb. It is capped and polyadenylated and its diameter is 80nm to 160nm. The Coronavirus genome confer a 5'-cap and 3' poly-A tail . Numerous eminent surface projections are present , they cover the viral surface completely, this gives them the crown like appearance. The size of the surface projection is about 20 nm. 2/3rd of RNA of coronavirus codes for non structural proteins and rest of it code for essential structural protein. [1,3]

ESSENTIAL PROTEINS:-

Spike proteins- The coronavirus spike protein is a type I glycoprotein that forms the peplomers on coronavirus particles. Coronavirus binds to specific cellular receptors through the spike protein. After the attachment of virus to the cellular receptor, the spike protein undergoes a conformational change which allows the fusion of viral membranes with the cellular membranes. The spike protein is vital for entry of virus, its cell-to-cell spread and for determination of tissue tropism. Spike is the major determinant of tropism and pathogenicity and is responsible for initiation of viral infection.

Membrane protein- This protein is present in abundance on the membrane. It plays a role in viral assembly and host intractions. Glycosylation of M proteins occurs for virus and host inyeraction. It can be N or O glycosylated.

Envelop protein- integral membrane protein. Plays important role in viral assembly.

Hemagglutinin esterase(HE) - HE glycoprotein ir responsible for formation of second type of spike on group II coronavirus. The second tupe of spike is smaller and allows binding of virus with sialic acid on host cell surface glycoprotein.

Nucleocapsid protein- Is a phosphoprotein which binds with viral RNA and act as a regulator for viral RNA synthesis. So this protein is essential for transcription and pathogenesis.

Replicase protein- They can determine the rate of viral replication so it affects tropism and pathogenesis.

Spike protein is a glycoprotein which exhibits high grade of mutation whereas in rest of the structural proteins no significat mutation is seen in COVID-19 . Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) when compared with severe acute respiratory syndrome coronavirus (SARS-CoV) showed less preserved models of Spike protein.

Its incubation period ranges from 1 to 14 days and its clinical features resembles to that of SARS-CoV and MERS-CoV that is cough, cold, fever, dyspnea, chest tightness etc . SARS-CoV and COVID-19 shows alike clinical features because both of them binds to angiotensin converting enzyme 2 (ACE2) receptor in lungs.[3,4]

EPIDEMIOLOGY:-

Origin – Zoonotic(most likely Bats) .

Intermediate host - Humans.

Spread of coronavirus occurs from one person to another via direct contact with an infected person or via droplet spread through coughing or sneezing.

The Reproductive ratio for COVID-19 is roughly between 2 to 4 . Reproductive ratio is degree of transmissibility which denotes the no. of people that can get infected from a single infected person.

Attack rate- 30- 40 %

Case fatality rate(CFR)- 3.4% worl wide

Timeline:-

- China notifies WHO on 2019-12-31
- First US case in Seattle 2020-1-15
- WHO declared pandemic on 2020-3-11
- National emergency on 2020-3-12

TRANSMISSION:-

It is a droplet infection, that is it spreads through tiny droplets released from nose and mouth of infected person when they cough or sneeze. The droplets can settle on the people around as well as on varoius surfaces. And the virus can spread if the virus enters the mucous menbranes of mouth or nose of the person who comes in contact with those infected surfaces. For how long the viruses will survive on any surface depends on its type. Surfaces can be disinfected within 1 to 2 mins by using 62% to 71% alcohol rendering the virus inactive.[1,5]

Viability of coronavirus on different surfaces:-

Airborne droplets-3hrs

Porous surfaces(cardboard, paper, fabric)- upto 24hrs

Hard, shiny surfaces(glass, countrertops, plastic, satinless steel)- upto 72hrs

So it is very important to have as less contact as possible with surfaces which could have been in contact with many persons and to follow proper hand washing and sanitising techniques to decrease transmission by fomites . Despite the fact it is not possible to avoid touching all the surfaces so the only option there is to avoid touching the mucous membrabes and to wash hands regularly. Alcohol based sanitisers and disinfectants can also be used to sanitise hands and surfaces respecitvely. There are few evidences suggesting feco-oral transmission. It has been found that stool might contain virus. And in such cases rectal swab comes positive

SARS-CoV2 is more transmissible than SARS-CoV, due to increased binding of spike proteins to ACE2 receptors as a result of mutation of spike protein.

PATHOGENESIS:-

SARS-CoV2 is a droplet infection . It means that it spreads via respiratory droplets which are released in the environment by coughing or sneezing. It can also spread via direct contact with an infected patient.

For binding of virus with host cell 2 receptors are needed ACE-2 receptor and TMPRSS-2(trans membrane protease serine precursor 2) receptor. After binding to these receptors membrane fusion and endocytosis occurs and endosome is formed. pH inside the endosome is acidic. Then uncoating of virus occurs and ssRNA is released. In the presensence of chymotrypsin like protease, translation occurs leading to formation of RNA dependent RNA polymerase and non structural proteins (NSP). The RNA dependent RNA polymerase enters the nucleus via importin channel and forms multiple copies of ssRNA . The ssRNA comes out and assemble with the NSP and forms the complete virus. The virus comes out of the cell via exocytosis. This causes activation of macrophages which causes release of cytokines like IL-6, VEGF etc. This leads to organ damage.

Through the mucosal membranes viral agent enters inside the body of host then it enters inside the respiratory tract , travels there finally enters alveoli in lungs. in the alveoli type II pnemocytes are present, they carry a receptor for SARS-CoV2 that is angiotensin-converting enzyme 2 (ACE2) receptor. SARS-CoV2 binds with ACE2 receptor. The binding occurs because of high affinity of S glycoprotein present on the outer membrane of the virus towards ACE2 receptor. After the binding is complete endocytosis of virus occurs inside the cytoplasm of type II pneumocytes. Following endocytosis the lysosomal enzyme breaks down the lipid bilayer of the viral agent.

The ribosomes of the host cell is utilised by SARS-CoV2 for translation of mRNA into polyproteins which then forms the structural framewok of virus.

Then initiation of self replication of polyproteins occurs which leads to an increase in the viral load in the patient. In the process of self replication SARS-CoV2 uses the RNA-dependent RNA polymerase present in the host. The polyproteins are then proteolysed by enzymes present in the host cell following which formation of various structural proteins like spike protein, E protein, nucleocapsid etc takes place. These proteins combines with the single stranded RNA which is formed by replication and forms the mature Virus.

The mature virus comes out of the type II pneumocytes by a process called budding. And during this budding the type II pneumocytes are destroyed. This destrution of type II pneumocytes causes realease of specific inflammatory mediators which then leads to stimulation of macrophages. The stimulated macrophages in respose releases specific cytokines like IL-1, IL-6 and tissue necrosis factor-alpha (TNF-α) . In case of acute inflammation IL-1 & IL-6 are released which causes fever. These specific cytokines enters the blood and causes contraction of the the endothelial cells of blood vessels and they also causes smooth muscle dilatation. These two actions results in an increase in capillary permeability which further leads to leak of plasma into the interstitial spaces finally causing alveolar edema. The other major problem that occurs due to type II pneumocyte destruction is decrease in surfactant production. This is one of the primary functions of type II pneumocyte. The surfactant is the substance which maintains the surface tension and prevent the collapse of the alveoli. But due to decrease in surfactant production surface tension increases causing alveolar collapse. Due to the alveolar collapse there is :- *Impairment of gas exchange. Due to this refractory hypoxaemia occurs.*

There is an extensive increase in the work of breathing due to imapired gas excahnge in an attempt to inspire as much air as possible against a collapsed alveolus as well as against interstitial edema. This mechanism leads to ARDS that is acute respiratory distress syndrome. Another feared complication alongside ARDS is disseminated intravascular coagulation. Disseminated intravascular coagulation (DIC) is what leads to the development of multi-organ failure .

During the destruction of type II pneumocytes inflammatory mediators are released they cause a neutrophil influx inside the alveolus. Neutrophils will destroy the virus by releasing reactive oxygen species and proteases. While destroying the virus the neutrophils causes destruction of all the alveolar cells as well.

Type 1 pneumocytes play an integral role in gas exchange so their destruction causes impairment of gas exchange. Type II pneumocytes produces surfactant so their destruction causes increase in surface tension which further leads to alveolar collapse. There is collection of fluid in the alveolus which consists of destroyed slough off cells and cellular debris that contains type I & II pneumocytes, macrophages & neutrophils resulting in formation of consolidation.The consolidation further interferes with the gas exchange, causing cough, dyspnea &hypoxemia . Hypoxaemia stimulates peripheral chemoreceptors causing the sympathetic stimulation leading to increase in rate of respiration and heart rate as a compensatory measure for decreased partial pressure of oxygen.

One of the most common complication seen here is systemic inflammatory response syndrome (SIRS). This is seen in case of progression of infection when the specific cytokines enters the vasculature causing increased capillary permeability . This increase in permeability of capillaries leads to leakage of plasma in the interstitial tissue spaces. This dumping of plasma in the extavascular space decreases the bollod volume.Also the vasodilataion that happened due to the cytokines further decreases the total peripheral resistance (TPR). The decrease in both the blood volume and TPR leads to a considerable drop in blood pressure that is hypotension . This leads to insufficient perfusion of organs and this can anytime progress to multi-system organ failure. Every organ manifest in its own ways . Elevation of blood urea nitrogen (BUN) and creatinine is seen in c/o insufficient kidney perfusion. This elevation is seen because kidney is unable to filter the needed amount of BUN and creatinine from blood and this finally causes acute renal injury and renal failure. The circulationg cytokines also enters the central nervous system CNS via the vascular system. The main site of action in CNS in hypothalamus. The IL 6 and IL 1 acts on the hypothalamus. Hypothalamus is the part of brain which maintains the body temperature. When IL-1 and IL-6 attains high concentartion in hypothalamus release of prostaglandins takes place and this disrupts the normal temprature of the body and resets the core body temperature to higher than normal resulting in fever. This means that one of the most universal and common sympton that is fever is caused due to elevated levels of IL-1 & IL-6.[1,3,5,6,7]

Clinical features:-

The duration between onset of symptoms and death varies from 6 to 41 days but it actually depends upon the age and immune status of the patient. The incubation

period is shorter among older individuals. India is still in better shape beacause the mortality rate is less compared to others.

Median timeline observed-

Day 1 – exposure to COVID-19

Day 5- presentation of 1st symptom

Day 10- dyspnea

Day 12- hospital admission

Day 13- ARDS

The people with comorbidities like asthma , diabetes and hypertension are at a higher risk. Other risk factors are patients on ACE inhibitors and ARBs as they cause upregulation of ACE-2 receptors. And this leads to an exponential increase in replication of the viral genome and it leads to increse in severity of the disease. And this also explains why people with hypertension are at a higher risk. This also explains the severity of infection in elderly as compared to younger people.

People at extreme of ages are at higher risk . Elderly people are at a comparatively higher risk because of the physiological change taking place in their lungs due to ageing. As age progresses the respiratory muscles get atrophied leading to reduction in respiratory functions. There is a significant decrease in lung capacity. Also the immune barrier becomes weak and the mucociliary clearance of the airway decreases. There is one more theory which suggests that with age no. of ACE2 receptors increases rendering the old people at higher risk of infection as compared to adults. Cardiovascular symptoms are also seen with COVID 19 patients. This is seen when the disease progresses and due to progression the immune system becomes defective. Myocardial injury also occurs due to cytokine storm as a result of imbalanced response between type 1 & 2 helper T cells.[8,9]

In the early phase the symptoms resembles common cold like cozyza , fever , cough and its difficult to diffrentiate but as the virus replicates and the viral load increases the severity of symptoms increase.

Damage to the alveolar epithelial cells causes fibrotic changes which leads to dyspnea, cough and hemoptysis. Multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs in some patients on hospital admission. Every person gives a varied response depending upon his immune status. So the severity of symptoms and the fate of disease directly depends upon the state of immune system of patient. This explains why elderly, immunodeficient people and people with comorbidities show severe symptoms and higher mortality campared to those who are comparitively healthy with a stronger immune status.

ACE 2 receptors are also present on enterocytes, so gastrointestinal symptoms can also be present. Technically as coronavirus is enveloped so it shouldn't have causes any GIT symptoms , but it does sometimes.

Generally in early stage the symptoms are not specific like fever, non productive cough , cold , bodyache, gneralised weakness lethargy with or without diarrhea. Patient may also complaint of difficulty in breathing that is dyspnea. As the disease progress hypoxia may develop leading to ARDS (acute respiratory distress syndome). In such situatuin mechanical ventiilation is given to the patient in ICU. Patients spO2 is closely monitored. And in such cases the chance of secondary bacterial pneumonia increase . the commonly involved organisms are staphhylococcus aureus, streptococcus pneumoniae, klebsiella pneumonia & hemophilus influenzae.

So the ***common symptoms*** are fever , dry cough, shortness of breath, myalgia , fatigue, sputum production, lymphopenia, nasal congestion ,chills /night sweats.

Uncommon symptoms are headache, hemoptysis, diarrhoea, confusion, rhinorrhea, chest pain , nausea , vomiting, sneezing.

Complications are Acute Respiratory Distress Syndrome (ARDS), secondary infection, ventilator associated pneumonia, septic shock, acute renal injury, hypoxemia, acute cardiac injury.[8,9,10]

EXTRAPULMONARY MANIFESTATIONS OF COVID-19:-

Neurologic – headache, dizziness, encephalopathy, ageusia, myalgia, anosmia, stroke

Renal – proteinuria, hematuria, acute kidney injury

Hepatic- elevated aminotransferases , elevated

bilirubin

Gastrointestinal- nausea, vomiting, diarrhea, abdominal pain, anorexia

Cardiac- myocardial injury, myocarditis, cardiac arrythmias, cardiogenic shock, myocardial ischemia, acute cor pulmonale, cardiomayopathy

Endocrine – hyperglycemia, diabetic ketoacidosis

Dermatological – petechaie, livedo reticularis, erythematous rash, urticaria, vesicles.

BIOCHEMICAL CHANGES:-

- CBC- leukopenia & lymphopenia
- Increase BUN
- LFTs- increase AST/ALT
- Increase D-dimer, increase CRP, increase LDH
- Increase IL-6, increase ferritin
- Decrease procalcitonin

INVESTIGATIONS:-

-LAB DIAGNOSIS:

1) Antigen detection- coronavirus antigen in respiratory epithelial cell can be detected by ELISA using specific monoclonal antibody

2) Electron microscopy- shows morphology

3) RNA detection by RT-PCR:- can detect RNA in respiratory secretions.

RT-PCR: it stands for reverse transcriptase polymerae chain reaction. Via reverse transcriptase DNA is formed fron the RNA of the virua and then it is amplified for detection.

4) Seum antibody detection by ELISA or hemagglutination.

- IMAGING:-

a) Chest Xray: hazy bilateral peripheral opacities

b) CT scan : ground glass opacities(GGO), crazy paving, consolidation.

CT sacn is not done in every patient. It is dindicated only in patient with moderate to severe symptoms and/ or worsening respiratory status.

CO-RADS

Standarised reporting system based on CT findings is CO-RADS. It gives the level of suspicion.

Table 1- This table shows CO-RADS which gives level of suspicion based on CT findings.

	LEVEL OF SUSPICION	**CT FINDINGS**
CO-RADS 1	NO	Normal or non-infectious abnormalities
CO-RADS 2	LOW	Abnormal findings consistent with infection other tha COVID-19
CO-RADS 3	INDETERMINATE	Unclear whether COVID-19 is present
CO-RADS 4	HIGH	Abnormal findings suspicious of COVID-19
CO-RADS 5	VERY HIGH	Typical COVID-19
CO-RADS 6	PCR +	

Typical appearance of COVID-19:- Peripheral bilateral ground glass opacities (GGO) with or without consolidation or visible interlobular lines (crazy paving). Multifcal GOG of rounded morphology with or without consolidation or visible interlobular lines (crazy paving). Reverse Halo sign (Atoll sign) or organising Pneumonia or spider web.

Indeterminate appearance:- multifocal , diffuse, peripheral or unlateral GGO with or without consolidation lacking a specific distribution and are non rounded and non peripheral. Very few small GOG.

Atypical appearance:- presence of isolated lobar or segmental consolidation without GGO. Discrete small nodules(cenrilobular, tree in bud). Smooth intelobular septal thickening with pleural effusion.

Very atypical appearance:- cavitation , calcification, tree in bud , bronchiolitis, nodular pattern.[11,12]

CT CHANGES OVER TIME:-

Table 2- This table shows CT changes seen in COVID-19 patients overtime

DURATION (DAYS)	STAGE	CHANGES
0-4	Early	GGO, partial crazy paving, lower no. of lobes involved
5-9	Progressive	Extension of GGO, increase crazy paving
10-13	Peak stage	consolidation
14 or more	Absorption	Gradula resolution

CT severity score:- scoring based on the % of each of 5 lobe involved. Each lobe is given individual score and then sum is calculated.

>5% involvement = score 1

5-25 % involvement = score 2

26-49% involvement = score 3

50-75% involvement = score 4

>75% involvement = score 5

Score ranges from 0 (no involvement) to 25 (maximum involvement).

if score <8 = mild

if score 9 to 15 = moderate

if score >15 = severe [13]

MANAGEMENT OF COVID-19:-

Symptomatic management, supportive care and prevention of transmission forms the mainsaty of management. Social distancing is the most affective tool we have to break the chain of man to man transmission. Most patients presents with mild to moderate presentation ranging from mild symptoms to mild pneumonia. And the patient with mild symptoms recover on their own with any medical interference , all that is needed for them to do is to isolate themselves to break the chain of transmission. Vitamin c & d , zinc, selium etc are being tried as measures to prevent from viral infections specifically respiratory .

Many drugs are under clinical trial . Hydroxochoroquine is being used widely in the treatment of COVID19 but there is no solid evidence to tell about its efficacy. And some studies even suggest that it is increasing the risk of cardiac arrest. REMDESIVIR is another drug under trail. Remdesivir inhibit viral replication. It is an adenosine analog. Multiple trials

are going on but no one drug has been narrowed down yet.[14,15,16,17]

Drugs under trial are :-

· Hydroxychloroquine- inhibit entry of virus by inhibiting ACE-2 & TMPRSS-2 receptor, inhibit endocytosis by increasing ph inside endosome.

· Nafamostat – TMPRSS-2 blocker

· Lopinavir , Ritonavir- protease inhibitor

· Remdesivir , Ribavirin, Favipiravir- RNA polymerase inhibitor

· Ivermectin – importin inhibitor

· Immunomodulators

a. corticosteroids, hydroxychloroquine

b. anti IL-6 – tocilizumab, sarilumab

c. anti VEGF- bevacizumab

d. plasma exchange

Control measures:-

- isolation of patient

- quarantine of exposed people

- travel restrictions if needed

- personal protective equipment- gloves, gowns,goggles etc.

- frequent hand washing with soap and water

- use of alcohol based sanitizer

- sanitization of surfaces which come in direct contact

- use of masks and shields at public places

- avoid personal contact with sick patient [18,19,20]

Conclusion

This is a review article on coronavirus in which I have dealt with its basic morphology, transmission ,pathogenesis , common clinical features and mangement. This is an emerging pathogen , not much information is present regarding this virus. It is primarily causes respiratory infection and spreads via droplet from person to person. Mostly is causes mild symptoms like cough , fever, cold , headache, loss of taste and smell. But in severe cases is can cause dyspnea , ARDS, pneumonia and even multi organ failure. It attaches to ACE 2 receptor and causes fluid dysregulation in the respiratory tract leading to alveolar edema leading to dyspnea. On CT scan ground glass opacities are a consistent finding. Mutiple drugs are under trial but no one drug has been proven 100% affevtive. Drugs like hydroxychloroquine, ivermectin , remdesivir etc are being used. Still the best remedy remains social distancing, sanitising and using personal protective equipment.

Material and Method

This is a review article . various artcles have been reviewed.

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