INTRODUCTION

Corona viruses affect different animals including human being. Nearly 50 years ago murine corona virus strain was first isolated in 1950, but its pathogenesis and replication was actively studied in 1970s\(^1\). Different animal viruses are of veterinary importance, like, porcine transmissible gastroenteritis virus (TGEV), bovine corona virus (BCaoV), and avian infectious bronchitis virus (IBV). At first corona viruses only produce self-limiting common cold in human being. But in spring 2003 this virus produced severe acute respiratory syndrome (SARS) epidemic occurred due to corona virus and it was coined as SAR-CoV. Again in 2012-13 another epidemic occurred in Middle East in the name of MARS-CoV, it was followed by small outbreak occurred in the same area due to mutation of this virus. In 2019, December this on-going epidemic started in Wuhan province of China and ultimately it has covered nearly 199 countries producing death of many people mainly elderly and with several comorbidities. In this review article the structure, pathogenesis, replication, clinical features and management of this virus have been described.

ABSTRACT

Corona virus, described in 1949 affected animals along with human being. In 1968 it was named Corona virus after observing the “CROWN LIKE” morphology of the virus under electron microscope. In 2002 -2003 severe acute respiratory syndrome (SARS) epidemic occurred due to corona virus and it was coined as SAR-CoV. Again in 2012-13 another epidemic occurred in Middle East in the name of MARS-CoV, it was followed by small outbreak occurred in the same area due to mutation of this virus. In 2019, December this on-going epidemic started in Wuhan province of China and ultimately it has covered nearly 199 countries producing death of many people mainly elderly and with several comorbidities. In this review article the structure, pathogenesis, replication, clinical features and management of this virus have been described.

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INTRODUCTION

Corona viruses affect different animals including human being. Nearly 50 years ago murine corona virus strain was first isolated in 1950, but its pathogenesis and replication was actively studied in 1970s\(^1\). Different animal viruses are of veterinary importance, like, porcine transmissible gastroenteritis virus (TGEV), bovine corona virus (BCaoV), and avian infectious bronchitis virus (IBV). At first corona viruses only produce self-limiting common cold in human being. But in spring 2003 this virus produced severe acute respiratory syndrome (SARS) epidemic was considered as “emerging pathogens” – this raised the question of the evolution and species of this coronaviruses (SARS-CoV). But since this epidemic two new strains have been recognised. Later on, a middle-east respiratory syndrome (MERS-CoV) was recognised in 2012 in middle-east areas.

Classification of coronaviruses

In 1968 the name “coronavirus” was coined after observing the “CROWN LIKE” morphology of the virus under electron microscope\(^8\). In 1975 International committee of Taxonomy of viruses established the family “Coronaviridae”. In June 2005, at 10\(^{th}\) International Nidovirus Symposium happened in Colorado Springs, Col., Coronaviridae has been subdivided into two subfamilies – coronaviruses and toroviruses. Toroviruses are responsible for producing enteric diseases in cattle and may be in human beings. Now Order “Nidovirales” composed of three families composing of “Coronaviridae”, “Arteviridae” (swine and equine viruses) and “Roniviridae” (invertebrates)\(^4\). “Nido” is the Latin word – means “Nest”. Hence the name of the order is Nidovirales. Different families of Nidovirales are differentiated based on number, type and size of the structural...
proteins which lead to significant alteration in the structure as well as morphology of nucleocapsid and virions.

Structure of coronavirus: Fig 1

It is round enveloped pleomorphic virion having diameter of 125 nm as demonstrated in cryo-electron tomography and cryo-electron microscopy\(^5,6\). There is multiple club-shaped spikes like projections released from the surface of the virus providing them the appearance of solar corona hence the name “corona virus”. There are helically symmetrical nucleocapsids within the envelope – it is more common in case negatively sensed RNA virus rather than among the positive sensed RNA virus. There are four viral proteins present on the membrane. These are:

1. **Spike protein (S)** (= 150kDa): Its N-terminal signal sequence is utilised to get access to endoplasmic reticulum and it is highly glycosylated. Homotrimeric class I fusion protein of this virion encoded S protein to make it spike like structure on the viral surface and it helps the virus to gain attachment with the receptor of the host cell\(^8,9,10,11\). In some cases of coronaviruses furin-like protease of host cell cleaves S protein into two polypeptides, S1 and S2\(^12,13\). S1 will be responsible for large receptor binding domain and S2 behaves like stalk of the spike\(^14\).

2. **Membrane protein (M):** Size is 25 – 30 kDa. This protein rolls the membrane three times and provides the proper shape of the virion. It has two domains:
   a. N-terminal ectodomain which is glycosylated.
   b. Larger C-terminal endodomain extending up to 6 – 8 nm into virion particle\(^15\).

According to recent study this protein exists in dimer form and will adopt itself to two different conformations thus leading to promote membrane curvature as well as attachment to nucleocapsid\(^16\).

3. **Membrane spanning protein (E):** It is a hydrophobic protein span the membrane twice\(^17\). It has short N-terminal ectodomain and C-terminal endodomain\(^18\). This protein has following functions:
   a. It has ion channel activity. In case SARS-CoV this activity is required for pathogenesis, not for replication\(^19\).
   b. It facilitates assembly and release of the virus.

In absence of this E protein as compared to other structural protein the lethality of the virion will be lost though it is virus type specific\(^20\).

4. **N protein:** It is the only protein in the nucleocapsid.
   a. It has both N-terminal and C-terminal ends, both of which can bind to RNA in different mechanisms but both the ends are required for binding of RNA\(^21,22\). Heavy phosphorylation of this protein triggers the structural changes in it which enhances the affinity of this protein for viral RNA in a beads-on-a-string formation\(^23\). There are two substrates on RNA to which this protein can bind – these are TRSs and genomic package signal – the last one has the affinity for C-terminal end of this N protein\(^24,25,26\).
   b. It also binds to key component of replicase, nsp3\(^27,28\).
   c. It also binds to M protein\(^29\).

Above protein interactions transform the viral genome to replicase-transcriptase complex which ultimately pack the encapsidated genome into viral particle.

5. **Hemagglutinin-esterase protein (HE):** It is present in subsets of β coronaviruses.
   a. It binds to sialic acid on the surface glycoproteins.
   b. It acts as hemagglutinin.
   c. It has acetyl-esterase activity\(^30\).

The above two actions help in S-protein mediated of that virion into the host cell and virion spreads through the mucosa\(^31\). But in case murine hepatitis virus this protein enhances neurovirulence\(^32\).

Viral genome: Fig 2

The genome contains 5’ structure at one end and 3’ poly (A) tail at the other end which acts as mRNA for translation of polyprotein replicase. There are seven genes in the RNA of the murine hepatitis virus (MHV). Replicase gene occupies 2/3rd of the genome present in the 5’ end of the genome and encodes non-structural proteins whereas rest genes 2 to 7 encode structural and accessory proteins. 5’ end have leader sequence, untranslated region has multiple stem loop like structure which is responsible RNA replication and transcription. On the other hand, 3’ untranslated region contains structures of RNA which is essential viral RNA synthesis. The sequence in the coronavirus is like this: 5’-leader-untranslated region (UTR) - replicase-S (spike protein)-E (envelope protein)-M (membrane protein)-N (nucleocapsid protein)-3’ UTR-poly (A) tail. If HE protein is expressed it will be encoded in 5’ to S. Accessory proteins are distributed within the structural genes at 3’ end of the genome. Untranslated regions of both the 3’ and 5’ ends of RNA where viral proteins react with host cells for replication of RNA in the form of positive and negative sense RNA. Within the two
open reading frames, ORF 1a and 1b replicate gene products are encoded. Via frameshifting process these two frames are translated into two large polyptides, pp1a and pp1ab. This frameshifting process involves pseudoknot structure – it is formed by RNA genome.

**Human corona virus**

To start with there are only two types of coronaviruses, OC43 and 229E responsible for common cold\textsuperscript{13}. There were some studies regarding the association of human coronavirus and multiple sclerosis, hepatitis and in case of new born enteric disease\textsuperscript{34,35,36}. In 2003, a new virus was isolated from the patients suffering from acute respiratory syndrome known as SARS-CoV\textsuperscript{37}. Since its identification two new coronaviruses were isolated. First one was isolated from the patient suffering from pneumonia and it was HKUI, group II coronavirus, but little is known about the biology of this virus as it was very difficult to propagate in the culture media\textsuperscript{38}. Second one was the HCoV-NL63, group I coronavirus isolated from 7 years old child of Netherland suffered from bronchiolitis associated with conjunctivitis\textsuperscript{39,40}. From there it was spreaded to Belgium, Canada, Hong Kong, Australia, Japan,\textsuperscript{41,42,43,44,45} All the patients have been suffered from upper respiratory symptoms, pneumonia and bronchiolitis\textsuperscript{45}. In case of children there was strong association between laryngeal croup and this virus\textsuperscript{46}. Again, this virus was isolated independently from children suffered from Kawasaki’s disease in New Haven, Connecticut—which was known as HCoV-NH\textsuperscript{37,48}.

**Life cycle of Coronavirus**

**Attachment of the virus with the host cell**

Viron attaches with the host cell through the interaction of S protein and host cell receptor. Receptorbinding domain site in the S1 region of S protein – which varies according to the virus\textsuperscript{49,50}.

a. In case of murine hepatitis virus (MHV) receptor binding domain (RBD) is present in the N-terminal S1 region.

b. In case of SARS-CoV virus this domain is present in the C-terminal S1 region.

**This S protein with host receptor interaction is responsible for**

a. Entry of virus into the host

b. Tropism of virus in the tissue.

**Different coronaviruses select different cellular receptors for their entry into the host.**

a. α-coronaviruses utilize aminopeptidase N as a receptor\textsuperscript{51}.

b. Transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV), feline infectious peritonitis virus (FIPV), canine coronavirus (CCoV) bind to aminopeptidase receptors\textsuperscript{52,53,54,55}.

c. SARS-CoV HCoV-NL63 utilize angiotensin converting enzyme 2 (ACE2) as their receptor\textsuperscript{56,57}.

d. MERS-CoV (Middle-east respiratory syndrome coronavirus) utilize dipeptidyl-peptidase 4 (DPP4)\textsuperscript{58}.

A. Entry into the host cells:

**Entry of the virion into the cell cytosol can be accomplished by following mechanisms**

1. S2 portion of S protein will be cleaved at two sites by acid dependent proteolysis by cathepsin, TMPRSS2 or another protease.

2. Cleavage at S2 exposes fusion peptide and it will be inserted into the membrane.

This is followed by joining of two heptad repeats in S2. This will form antiparallel six-helix bundle\textsuperscript{10}. This bundle formation helps in mixing the viral and host cell membrane leading to fusion of both the membrane and thus release of viral RNA in to the host cell cytoplasm.

**Expression of replicase protein**

In this stage there is translation of replicase gene from the viral genomic RNA. This replicase gene encodes two open reading frames – rep 1a and rep 1b expressing two co-terminal polyprotein, like, pp 1a and pp 1ab. Virus can express both polyprotein by utilizing two methods – one is slippery sequence (5′-UUUAAAC-3′) and the other is RNA pseudoknot. Both of them helps to produce frameshifting from rep 1a to rep 1b of open reading frame by unwinding pseudoknot. Sometimes this pseudoknot prevents ribosome from elongation and thus will stop slippery sequence. In that case backward shifting for one nucleotide (- frameshift), in the meantime ribosome melts and unwind the pseudoknot and helps in normal propagation of the polyprotein to reach rep 1b – which ultimately results translation of pp 1ab\textsuperscript{60,61}. It is not exactly known why the frameshifting and pseudoknot are required by the virus for translation, but it may be due to following reasons:

a. It controls the rep 1a to rep 1b ratio

b. It will delay the products of rep 1b until the proper environment will be created by rep 1a for RNA replication\textsuperscript{62}.

Polyprotein pp 1a contains 1 – 11 non-structural protein (nsp5) and pp1ab contains 1 – 16 nsp5. After extension of pp 1a to pp 1b nsp 11 becomes nsp 12. Then these polyprotein are cleaved into individual nsp5s by different proteases. There are:

a. Papain like protease (PLpro) is encoded by nsp3 – it will cleave nsp1/nsp2, nsp2/nsp3, and nsp3/nsp4 boundaries.

b. Main protease (Mpro) is encoded by nsp5 --

Most of the coronaviruses encode two PLpro within nsp3, but γ-coronavirus, SARS-CoV, MERS-CoV encode only one PLpro within nsp3\textsuperscript{63}.

Now many nsp5s assemble to form replicase-transcriptase complex which will make an environment for RNA synthesis followed by RNA replication as well as transcription of subgenomic RNA. For replication of RNA nsp5s contain several domains for enzyme. These are:

a. Nsp5 12 responsible for encoding RNA dependent RNA polymerase

b. Nsp5 13 is responsible for encoding RNA helicase domain RNA 5′ triphosphatase activity.
c. Nsps 14 is responsible for encoding 1. exoribonuclease which is involved in replication fidelity and 2. N7 methyltransferase activity
d. Nsps 16 is responsible for encoding 2-O- sferase activity methyltranOther activities of nsp are:

**Blocking of innate immunity response**

Nsps3-ADP-ribose-1″-phosphate and nsp5-endoonuclease activity. The last activity is the unique for Nidovirales order\(^6^4\).

**Replication and transcription: Fig 3**

Sub-genomic and genomic RNAs are produced as a result of viral RNA synthesis through negative-strand intermediates which is only 1% as compared to its positive counterparts. Sub-genomic RNAs act as mRNAs structural and accessory genes. Positive sense is present at 3′ coterminol with full length viral genome thus forming a set of nested RNA – it is distinct property of Nidovirales.

Replication of RNAs requires cis-sequences. 5′UTR contains seven stem-loop structures which extends into 1a replicase gene\(^65^6^6\). On the other hand, 3′terminal UTR contains a bulged loop structure, a hypervariable region and pseudoknot but stem loop and pseudoknot cannot be formed simultaneously but may overlap\(^67^6^8\). So different structures are responsible for alternate stage of RNA synthesis but which stage is being regulated by what mechanism – it is unknown.

The novel character of coronavirus is the fusion of leadership sequence and body transcriptional regulatory sequences (TRSs) which is believed to occur during the phase of discontinuous extension of negative strand\(^6^9\). According to current thinking regarding the existing model if there is pause of RNA-dependent RNA polymerase (RdRp) at any place of the body of TRS sequences (TRS-B), after this pause whether it continues the process of elongation to next TRS or it tries to amplify the leadership sequences at 5′terminal completely under guidance of complementarity of TRS-B TO TRS-L.

But there are many unanswered questions, like, the method by which the RdRp bypasses the TRS-B sequences, or the method by which TRS-B sequences is being directed towards TRS-L sequences and with how much complementarity. The unique ability of the coronavirus is their ability to recombine by using non-homologous and homologous recombination by the switching ability of RdRp – which is the basis of viral evolution as well as for targeted RNA recombination\(^7^0^7^1\).

**Assembly**

After the synthesis of the subgenomic RNAs different structural proteins are translated, moved along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). M protein is very important in protein to protein interactions required for assembly of coronaviruses. But when M protein and E protein are expressed simultaneously virus-like particle (VLP) is formed – it suggests that these two proteins are absolutely necessary for formation of viral envelope\(^7^2\). N protein produces fusion of encapsidated genome with ERGIC thus enhancing the envelopement\(^7^3\). On the other hand, S protein is not required for assembly but interact with M protein for incorporation thus trafficking to ERGIC. There is abundance of M protein as compared to E protein, hence it has been suggested that M protein is required for maturation of viral envelope. But several hypotheses are present regarding the role of E protein in viral envelope maturation:

A. It induces curvature of envelope\(^7^4\).
B. It prevents the M protein aggregation\(^7^5\).
C. It helps in release of virus by altering the secretary pathway\(^7^6\).

M protein interacts with N protein at the C terminal end of the former with the C terminal domain 3 of the later protein, but the exact process by which N protein complexes with RNAs and progress towards ERGIC to interact with M protein is till unknown.

**Release**

After assembly the complete virion particle is transported to the cell surface and gets released by exocytosis. S protein, in case of many coronaviruses, does not get assembled during transit to the cell surface rather it helps in fusion between infected cell with the adjacent uninfected cells. As a result, there is formation of multinucleated giant cells allowing the virus to spread in the infected organism without being detected or neutralized by the protein specific antibodies.

**Origin of SARS-CoV**

Before the outbreak of SARS-CoV this virus produced only mild respiratory illness in human. Two α-human coronaviruses are HCoV-229E and HCoV-NL63 and two β-human coronaviruses are HCoV-OC43 and HCoV-HKU1\(^3^8^3^9^4^0\). Amongst them HCoV-229E and HCoV-OC43 were discovered 50 years ago but the other two were isolated during SARS-CoV outbreak\(^3^5\). SARS-CoV, HCoV-NL63 and HCoV-HKU1 produced more severe disease in case of neonates, elderly and people with severe morbidity. Most important in these viruses are their genetic variability in the same location. As for example, HCoV-229E isolated from different parts of the world showed minimal genetic variability, where as HCoV-OC43 isolated from same location demonstrated significant genetic variability\(^7^7^7^8\).

SARS-CoV produced a outbreak of severe acute respiratory syndrome in 2002—2003 in Guangdong province of China, infected 8098 persons, 778 patients died with mortality rate of
9%, in case on elderly patients it was increased up to 50%. It was started in a hotel in Hong Kong, since then it spreaded over two dozen of countries with loss of nearly 40 billion dollars of economic activity with total lock down the activities in South-East Asia, Canada for several months. It was originated in Chinese horseshoe bats because sequences of SARS related CoV serological evidence of prior infection were found in them 79,80. It was also demonstrated that those viruses used ACE2 in bats as that used by human coronavirus. Again, there was serological evidence of SAR-CoV infection found in the asymptomatic persons in the wet animal market81. Hence it is likely that this virus was in the circulation for several years prior to spread of this virus in a large population in opportunistic conditions. There was evidence of 99% homology between SARS-CoV isolated from animal and human being in 2003. The only difference is deletion in OPEN READING FRAME 8 which differed in length. It was not known this loss of whole ORF 8 region was responsible for adaptation in human being or it was dispensable in human being82. So, it was the area from where interspecies transfer of animal virus to human beings. According to one study SARS-CoV is inefficient in infecting human being, only repeated exposure to the infected animals may lead to abortive infection in human leading to development of positive serological response in in animal handlers83. Most of the transmission occurred through direct contact with households and healthcare individuals, but few cases super spreading occurs into the community due to firstly, enhanced effect of heavy burden of virus and secondly, increased aerosolization of the virus. Due to its inefficient transmission to the community it was controlled by quarantining at that time. Molecular epidemiological studies demonstrated repeated introduction of animal coronaviruses into human beings. In the early epidemic, December 2003 in Guangdong province, China isolated SARS-CoV was much closure to palm civet coronavirus as compared to other coronavirus isolated in early epidemic84, 85. Reservoir of SARS-CoV were wild animal, domestic cat and ferrets, bats birds, dogs and foxes86,87,88,89. After the discovery of ACE2 receptor having affinity for coronavirus it was understood that SARS-CoV enters into these cells followed by interspecies transmission at molecular level77. According to some studies spike protein from the outbreak 2003-2004 and palm civets only involved ACE2 cells rather than cells expressing human receptor as compared to the spike protein from more severe outbreak 2002-2003 involved both ACE2 cell and human receptors containing cell71,90,91. After discovery of SARS-CoV it was placed in a new group – group IV92,93. But after observing the ORF 1a domain of SARS-CoV is unique to that of group II, since then it was put into group II and it is more related to bovine coronaviruses, murine coronaviruses and human OC4394. According to different bioinformatics SARS was the result of several recombinant events. According to one study it was the result of SARS-polymerase recombination77. Again, according to other study SARS was the result of recombination between mammalian and avian parent viruses – replicase protein of mammalian origin and matrix and nuleocapsid protein of avian origin spike protein of both mammalian-avian origin78. But it seems unlikely that SARS was the result of mammalian-avian virus recombination. The hallmark of coronaviruses is recombination and it is major force of evolution of coronavirus.

### Resilience of coronaviruses in different environments

<table>
<thead>
<tr>
<th>Environments</th>
<th>Temperatures</th>
<th>Survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>50° – 59° F</td>
<td>4 hours</td>
</tr>
<tr>
<td>Nasal mucus</td>
<td>77° F</td>
<td>2 – 3 minutes</td>
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<tr>
<td>Droplets</td>
<td>132.80° F</td>
<td>Half an hour</td>
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<tr>
<td>Hands</td>
<td>Less than 77° F</td>
<td>24 hours</td>
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<td>Non-woven fabric</td>
<td>680 F – 860 F</td>
<td>Less than 5 minutes</td>
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<tr>
<td>Wood</td>
<td>500 F – 590 F</td>
<td>Less than 8 hours</td>
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<tr>
<td>Stainless steel</td>
<td>500 F – 590 F</td>
<td>48 hours</td>
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<tr>
<td>Alcohol</td>
<td>75%</td>
<td>24 hours</td>
</tr>
<tr>
<td>Bleach</td>
<td></td>
<td>Less than 5 minutes</td>
</tr>
</tbody>
</table>

### Pathogenesis of SARS-CoV

SARS as proposed was composed of three phases – first, viral replication, second, immune hyperactivity and third, pulmonary destruction80. Lung pathology consists of:

A. Diffuse alveolar damage
B. Proliferation of epithelial cells
C. Multinuclear giant cells infiltrate of macrophages.
D. Putative syncytium-like formation associated with multinuclear infiltrate macrophages and epithelial cells – characteristic of coronavirus80.
E. Hemophagocytosis in the lung – it supports cytokine dysregulation87.

### In the intestine SARS-CoV

A. Viral replication
B. No disruption of intestinal cellular architecture.
C. Absence of intestinal inflammation – it is the result of up-regulation of transforming growth factor β and apoptotic response of intestinal epithelial cells96,97.

According to recent evidences SARS is a widespread disseminated systemic disease, hence virus can be shaded through the following secretions100,101:

A. Respiratory secretions
B. Stool
C. Urine
D. Sweat

In the alveoli stimulated macrophages produces pro-inflammatory cytokines in the alveoli. According a in-vitro study SARS infected macrophages induces viral replication, protein synthesis, but all ae abortive and ultimately no viral particle was produced, on the other hand, in case of HCoV-229E there was chemokine response but without any IFN-α/β response102. SAR-CoV replicate in the mononuclear cells in the affected patients. According to one study analysis of gene expression profiles of SARS-CoV in peripheral blood mononuclear cells from 10 defined patients demonstrated that the response was innate immune response rather tan a specific response against virus103. The authors of that study did not find any major cytokines, like, interferon, major histocompatibility complex class 1 gene and genes responsible for complement mediated cytolysis. So, their conclusion was the immune response of SARS-CoV was different from other viral infection.
Lymphopenia along with increasing viral load – itself suggests immune evasion by this SARS-CoV. According to one study following evasion immune response seen in SARS-CoV infected primary myeloid derived dendritic cells:104;

A. Low expression of antiviral cytokines, like, INF-α, INF-β, INF−γ and IL-12p40. 
B. Moderate upregulation of proinflammatory cytokines, like, tumor necrosis factor-α, interleukin-6. 
C. Significant upregulation of proinflammatory cytokines, like, RANTES, IP-10. 

There may be rapid decrease of CD4 and CD8 T lymphocytes – it may be associated with death of the patient. Since there is no ACE2 expression in lymphocytes, hence lymphopenia in SARS-CoV may be due to apoptosis of uninfected lymphocytes. 

By 2003 SARS-CoV epidemic was controlled, but again one new strain of human coronavirus emerged to produce a new epidemic in Middle east in Saudi Arabia and other countries in the name of Middle-east respiratory distress syndrome coronavirus (MERS-CoV) which involved respiratory tract with 50% mortality rate. It was controlled to some extent, but in 2013 few sporadic cases continued. Again, in 2014 repeated outbreak occurred in the same area suggesting mutation of the virus and human to human transmission. According to European Centre for Disease Prevention and Control as on 27th August, 2014, total cases were 855 with 333 deaths and mortality rate of 40%. MERS-CoV is group 2c β-coronavirus being highly related to HOKU4 and HKU5.105. The most common manifestations were fever, cough, shortness of breath, tremor, myalgia, gastrointestinal symptoms, like, nausea, vomiting and abdominal pain. Severe cases may develop respiratory failure requiring mechanical ventilation, renal shut down, septic shock and eventually death. According to the previous belief bats was the primary host and human being was the intermediate host when they were infected with bat’s excreta. But later on, antibodies to this virus was found in the blood of dromedary camels in the middle East suggesting that dromedary camel was the natural host. Few studies demonstrated that identical antibodies were also found in the human and camel blood nearby Saudi Arabia – one study demonstrated direct contact of human being with the infected camel, in that case identical virus as well as identical antibodies was found.106, 107. So, it has to be determined that how many cases of MARS-CoV cases are due to direct human to human transmission and in how many cases human being were intermediate host in that outbreak. This virus utilises the DPP4 receptors in bats, camels, rabbit, human being and horses but not of mouse because of the different structure of DPP4 in mouse making it impossible to produce any vaccine or antivirals against this virus. But recently adenoviral vector has been utilized to introduce DPP4 gene into the lungs of mouse and thus it is possible to do any intervention for production of antiviral drugs or vaccine in any animal that is sensitive to adenoviral transduction.

Diagnosis

Since viral disease is a self-limited infection and runs its natural course diagnosis of coronavirus is unnecessary but in case severe outbreak even in case of veterinary outbreak diagnosis of the virus is most important to control the pathogens, to protect food supplies and to protect human community. Only multiplex real-time polymerase chain reaction (RT-PCR) can diagnose all four coronaviruses:108,109.

Treatment

Though interferon with or without ribavirin have increased activity against the coronaviruses but in vivo requires further evaluation.110. The disease can be prevented by vaccine. Vaccines against IBV, Canine coronavirus and TGEV have been approved but these are not used because it may not be effective in certain circumstances. Vaccines against veterinary coronavirus PEDV is very useful to prevent its spread to anew locations. Live attenuated vaccine developed from attenuated variant PRCV protected TGEV since 1980s, so only mild disease was developed in swine but severe disease was prevented for last 30 years. But this vaccine faced several challenges, like firstly, Natural infection does not prevent subsequent infection thus this vaccine must induce better immunity as compared to natural virus infection, secondly, Potential development of diverse recombinant virus111 thirdly, Vaccination with the spike protein may lead to disease enhancement.112 So, vaccine should be developed to reduce the chance of recombination, like:

A. Deletion of non-structural proteins 
B. Deletion of envelope protein E 
C. Rearrangement of protein at 3’ end of the genomic RNA. 
D. Use of variant of virus or mutant virus 
E. Modification of transcriptional regulatory sequences

Evaluation and treatment of COVID-19:

Viral diseases occur as large outbreak, like, SARS-CoV in China in 2003 – 2004, H1N1 influenza in 2009, MARS-CoV in Middle East area in 2012 – 2013 with a small flare-up in 2014 by its mutant in the same area. Another one developed in December 2019 in China. It was first detected as epidemic cases of lower respiratory tract infections in largest Metropolitan area, Wuhan, Hubei Province and reported in the local office of WHO, in China in December 31, 2019. During that time, they were unable to detect the agent and these cases were classified as “Pneumonia of unknown etiology”. They started searching the causative agent and ultimately declared these cases occurred due to a novel virus of coronavirus family and named as COVID-19 (CO – Corona, VI- Virus, D – Disease, 19 – started in 2019) – as announced by Director General of WHO, Tendros Adhanom Ghebreyesus on February, 2020. Now COVID-19 is pandemic involving 199 countries throughout the world. In February 26th, China though it was initially named as 2019-nCoV but it is declared as SARS-CoV-2 by Experts of International Committee on Taxonomy of viruses as it is very closely similar to that SAR-CoV.

Coronaviruses are isolated from different animal species but can cross the interspecies barrier to infect respiratory tract of human being. COVID-19 ultimately crossed the interspecies barrier to infect human being and became a pandemic disease. The number of Scientists around the world work on their structure, transmission mechanism, clinical spectrum of the disease, process of diagnosis and try to establish a therapeutic as well as preventive counterpart to remove them from the
grass root. But many things are uncovered, like, interaction between host and virus, timing and evolution of epidemic.

**Etiology**

Sub-family of Coronaviridae is Orthocoronaviridae are classified into four genera. These are

A. Alpha-coronaviruses
B. Beta-coronaviruses: This is classified into five sub-genera\(^ {113} \).
C. Delta-coronaviruses
D. Gamma-coronaviruses

Bats and rodents are the gene sources of alpha and betacoronaviruses, whereas, avian species are the main gene sources of delta as well as gamma-coronaviruses. All these CoV produce respiratory tract infection, neurologic, enteric and hepatic involvement in cats, bats, cattle and camel. Few human CoV are identified till date, some of them are detected in the 2020. 2% human are the healthy carrier and nearly 10% presents with acute respiratory tract infection\(^ {114} \).

HCoV-OC43, HCoV-HKU1 (beta-coronaviruses) and HCoV-229E and HCoV-NL63 (alpha-coronaviruses) are responsible for common cold with upper respiratory tract infection in immunocompetent patient and in case of immunocompromised and elderly patient, lower respiratory tract infections. SARS-CoV and MARS-CoV (beta-coronaviruses) are responsible for different epidemics with variable involvement of different systems in the body with mortality of 10% and 35% respectively. SARS-CoV-2 is round or elliptical or pleomorphic form having diameter of 60—140 nm, it is sensitive to ultraviolet light and heat, can be inactivated in ethanol, ether, peroxycetic acid, chlorine containing disinfectant, chloroform but never in chlorhexidine. Genetic distribution of new HCoV isolated from the patients of Wuhan has 89% nucleotide similarity with that of bat SARS-like-CoVVZXC21 and 82% similarity with human SARS-CoV\(^ {115} \). It has 29891 nucleotides which encode 9860 amino acids. Analysis of genetic sequences suggests that this virus has been evolved from a strain in bat, but the intermediate source responsible for transmission from bats to human is not discovered yet. But sudden mutation in this strain found in bats may act as direct triggering factor to human.

**Transmission of the virus**

First case of SARS-CoV-2 was detected from the direct exposure of Huanan sea food in the Wuhan market, but no further case was isolated from such exposure suggesting human to human transmission from symptomatic or asymptomatic people as asymptomatic people may transmit virus. It signifies isolation may be the best process of preventing the spread of virus. There are several processes of transmission. These are:

A. through respiratory tract in the form of soughing and sneezing and talking.
B. Aerosol transmission: In case of closed space transmission through aerosol droplet as the droplets will remain in the air for some time. As the droplets are suspended in the air, it will lose its water. So, the pathogen only forms the core of the droplet. The droplets can fly for long distance and transmit. But till now there is such evidence yet.
C. It can also spread through feco-oral route, because virus was isolated from the stool if the infected persons.
D. Through indirect contact: If air droplets will be deposited in the table or any surface from where it will be transmitted through the contaminated hand as the virus can pass to the mucosa of the eyes, oral mucosa, nasal mucosa.
E. Mother to child transmission: There was evidence that one child became throat swab positive for this virus suggesting that it was neonatal infection through mother to child transmission.

**Following factors are responsible for susceptibility to this novel virus**

A. New antigenicity of the mutant virus.
B. Amount of exposure. In case of heavy exposure person with good immune function may get infected.
C. Elderly people
D. Pregnant women
E. Chronic kidney disease
F. Chronic liver disease
G. Immuno compromised patient
H. But the main factor is the chance of exposure. After an exposure a person may not be infected. Again, child has very low chance of infection from the exposure but this is not true that this group will never be infected. It is commonly prevalent in winter as well as in spring.

**Epidemiology**

**There are three stages spread in this epidemic. These are**

A. Local outbreak – In this stage cases were due to exposure to seafood market.
B. Community communication – It means interpersonal and clustering transmission
C. Widespread stage – It means that this disease has already been spreaded to entire China and throughout the world.

The spread in China was basically between infected persons and health professionals, heath-workers, family members and other close contacts. Based on China CDC and local CDC data incubation period was 3 to 7 days may be up to 2 weeks with longest time from the onset of infection to appearance of symptoms was 12.5 days\(^ {116} \). In some reported cases the incubation period can extend up to 28 days.According to their data there was doubling of this epidemic every week with basic reproduction rate of 2.2 i.e. one affected patient can transmit additional 2.2 individual whereas basic reproduction number in 2002 – 2003 due to SARS-CoV epidemic as 3\(^ {117} \). But till today we throw full light on the mechanism of transmission, incubation period, infectivity duration and clinical course. Both infectivity and lethality are required for a virus to produce any harm. SARS-CoV-2 is highly infectious but its lethality till today cannot be determined.

Main average interval from the onset of the disease to the initial hospital visit was 5.8 days and from the onset of the disease to hospitalization was 12.5 days for mild cases, but in
severe cases the last one was 7 days only. In fatal cases onset of the disease to diagnosis was 9 days and from the onset of the disease to death was 9.5 days.

In China there are 81,021 clinically and laboratory confirmed cases with 3,173 death. Till today 199 countries have been taken up by this virus. On 28th February 2020 it was declared as epidemic but today 29th March SARS-CoV-2 total number of cases is 680,696, recovery of 146396 and death of 31920, active cases are 502380 with mildly involved cases are 476958 (95%) and 25,422 (5%) severe cases. Highest number of cases occurred in USA (123, 781) followed by Italy (92472), China (81,439), Spain (78,797), Germany (58247). This virus is epidemic for several reasons:

- A. Mutation in the coronavirus makes it new to the human being since that person is lack in immunity against that mutated virus.
- B. There more than one route of transmission.

Pathogenesis

How this virus produces pneumonia is very complex which was not explained with all aspects through research. But as far data are available, it is able to produce an excessive immune reaction, known as “CYTOKINE STORM” the effect of which is extensive tissue damage. The prokinetic factor in this damage is interleukin-6 (IL-6) produced by active leukocytes. IL-6 acts on large number of cells and produces following effects:

- A. It will promote differentiation of B lymphocytes
- B. It will promote the growth of some categories of cells while inhibit the growth of other cells.
- C. It will increase the production of acute phase protein.
- D. It will control the thermoregulation.
- E. It will maintain the functionality of central nervous system.
- F. It has also some anti-inflammatory effects.
- G. It has an implication in the pathogenesis of cytokine release syndrome which is characterised by fever with multiorgan dysfunction.

Clinical features

Clinical features have a wide spectrum of presentations – at one end of the spectrum there are presence large number of asymptomatic cases and at the other end there are cases of septic shock with multiorgan dysfunction syndrome and in between there are mild to moderate and nearly severe cases. In one study, Huang et al. demonstrated total 41 cases with fever, dry cough, respiratory distress with abnormal computerised scan findings in chest – one third of cases (13.32%) required intensive unit care and 15% were fatal118. In another study, Li et al. demonstrated in first 425 cases there were no gender and sex (male-56%) difference, median age of infected person was 59 years with ranges from 15 to 59 years and no incidence occurred below 15 years119. In 20th February, 2020 Chinese CDC shared data of 72314 with Journal of American Medical Association where it was shown that 62% were positive data including 1% asymptomatic but laboratory-positive data, case fatality rate of 2.3%, fatal cases included age distribution of ≥80 years (15%), 70 –79 years (8%) and co-morbid cases are 49%. But 1% were below 9 years without any fatality.

Definition of SARI

1. It can be defined as upper respiratory infection with high fever or measured temperature ≥38°C and cough having onset within last 10 days requiring hospitalization with no other etiology which fully explains the clinical presentation AND any one of the following:
   - a. History of international travel within 14 days prior to onset of symptoms.
   - b. Disease occurs in health care worker who has been working in an environment where patient with severe acute respiratory infections are being cared for, without regards to place of residence or history of travel.
   - c. Person develops unusual and unexpected course, mainly sudden deterioration in spite of appropriate treatment, without regards to place of residence of history of travel, even if another etiology has been identified which fully explains clinical presentation.

2. Patient with acute respiratory illness of any severity who, within has following exposures within 14 days of onset of illness:
   - a. Close physical contact with a confirmed case of SARS-CoV-2 infection while the patient was symptomatic.
   OR,
   - b. Healthcare facility in a country where hospital-associated SARS-CoV-2 infection has been reported.

Clinical syndromes ASSOCIATED WITH covid-19 infection:

A. Mild cases (81%): These are sufferer of mild pneumonia or non-pneumonia. Symptoms are:
   - 1. Headache
   - 2. Bodyache
   - 3. Mild fever
   - 4. Sore throat
   - 5. Nasal congestion
   - 6. Myalgia
   - 7. Diarrhea in few cases.

But never respiratory distress, sepsis or signs of dehydration as this symptom will allow the patient into severe stage.

B. Mild pneumonia:
   - 1. Patients with sign of mild pneumonia but not severe.
   - 2. In case of child with non-severe pneumonia with cough and difficulty in breathing/fast breathing:
      - a. Less than 2 months -- >60/minute
      - b. 2 – 11 months -- ≥50/minute
      - c. 1 – 5 years -- ≥40/minute
      - d. No sign of severe pneumonia.
   - C. Severe cases (14%): This stage is characterised by:
      - a. Respiratory distress
      - b. Respiratory rate is ≥30/minute
      - c. Blood oxygen saturation (SpO2) ≤90% at room air.
      - d. Ratio of Partial pressure of oxygen (PaO2) Percentage of oxygen supplied (FiO2) is <300

Lung infiltrate >50%

In children: Cough with respiratory difficulty with any one of the following:
   - a. Central cyanosis
   - b. SpO2 <90%
   - c. Severe respiratory distress, like, chest indrawing
   - d. Signs of pneumonia with any one of the following:
     - Inability to breastfeed or drink
Lethargy or unconsciousness or convulsions
- Other signs of pneumonia
  - Indrawing of the chest
  - Fast breathing <2 months ≥60/min, 1–5 years ≥50/min, 1–5 years ≥40/min
  - Chest x-ray to exclude any complication

These cases are mainly severe pneumonia, sepsis, septic shock.

The percentages of patients till be defined, will enter the critical phase suddenly within a week.

- Critical cases (5%):
  - This stage includes the complications of this disease, like, multiorgan dysfunction or failure, septic shock, respiratory failure
  - Acute respiratory distress syndrome (ARDS): This diagnosis includes both clinical and ventilatory criteria. It may present as acute onset severe respiratory failure or worsening of already existing respiratory failure. Reference parameter is PaO2/FiO2.
    - a. If it is >200 but <300 mm of Hg – it is mild ARDS
    - b. If it is >100 mm of Hg but <200 mm of Hg – it is moderate ARDS.
    - c. If it is <100 mm of Hg – it is severe ARDS.
  - In case of nonavailability of PaO2 SpO2/FiO2 ≤315 – suggests severe ARDS (including in non-ventilated patients)

Bilevel NIV of CAP ≥5 CM H2O via full mask: PaO2/FiO2≤300 mm of Hg. Or SpO2/FiO2≤264
- In case of mild ARDS (invasively ventilated): 4≤O1<8 or 5≤OSO<7.5
- In case of moderate ARDS (invasively ventilated): 8≤O1<6 or 7.5≤OSI<12.3
- In case of severe ARDS (invasively ventilated): O1≥16 or OSI≥12.3.

Oxygenation (children, note OI = Oxygeneation index, OSI = Oxygenation index using SpO2)
- CT scan of chest demonstrated more than 50% of lung bilaterally was filled up with exudates. In some case clinical presentation with ventilatory data may simulate pulmonary edema with left ventricular failure, in those cases cardiac failure has to be excluded and if required echocardiography has to be done to exclude cardiac cause.

Sepsis
- According to International Consensus definition of sepsis and septic shock (sepsis-3) it can be defined as life-threatening organ dysfunction by a dysregulated immune response to infection. Organ dysfunction can be addressed when there is acute change in SOFA score ≥2 – it suggests mortality risk of 10% in general hospital population. In case of SARS-CoV-2 clinical picture of sepsis is serious, like, severe dyspnoea, hypoxemia, reduced urine output, altered mentation, tachycardia, hypperbilirubinemia, high lactate (>2 mmol/L or 18 mg/dl), acidosis, coagulopathy, thrombocytopenia.

- In case of children, with suspected or proven infection, ≥2 SIRS criteria – one must be abnormal temperature or abnormal white blood cell count.

Septic shock
- In case of adult: Persistent hypotension in spite of adequate volume resuscitation and requirement of vasopressor to maintain mean arterial pressure to ≥65 mm of Hg and serum level of lactate <2 mmol/L.

- In case of children any hypotension (systolic blood pressure <5th percentile or ≥2 SD below the normal for age) or 2 – 3 of the following:
  - A. Altered mental state
  - B. Bradycardia (<90/minute in infant or <70/minute for children) or tachycardia (>160/minute in infant or <150/minute for children)
  - C. Prolonged capillary refill time (>2 seconds) or petechial purpuric rash
  - D. Increased serum lactate level
  - E. Oliguria
  - F. Hyperthermia or hypothermia

Peculiarity of this new disease as compared to other viral or bacterial diseases
- This disease has some special characteristics. All the patients present with fever not so responsive to antipyretics, malaise and dry cough. In case of fragile patient shortness of breath may start from onset.

- After 5 – 7 days older patient with unstable lung develops rapid respiratory rate and shortness of breath. On the other hand, younger stable patients without any co-morbidities may develop the shortness of breath later. After few days there will be gradual decrease in oxygen saturation to less than 90% -- this is most crucial phase as the patient from this stage patient may develop rapid deterioration of respiratory function, asymptomatic patient may slightly hypoxic requiring oxygen therapy. In the next stage noninvasive ventilation may be required to increase PiO2/FiO2. In few cases in front of the eyes of the operator the patient may collapse and requires mechanical ventilation. After continued mechanical ventilation patient may improve within 24-48 hours, but one should not try to wean at that time because, after initial improvement there may be again worsening of the respiratory symptoms requiring reintubation. Hence it is advised to keep the mechanical ventilation for 1 – 2 weeks.

Evaluation of the SAR-CoV-2 patients
- Clinical presentation and the epidemiological factors have to be evaluated to detect whose blood is essential for sending for viral testing. US CDC have made a guideline for the suspected persons, named, Persons under Investigation (PUI) for COVID-19. According to that guideline:
  - A. Persons who developed fever along with acute respiratory illness, like, cough, difficulty in breathing.
  - B. Following epidemiological factors:
    - a. Persons who are in close contact with the laboratory proved COVID-19 within 14 days.
    - b. History of travel to the epidemic areas within last 14 days from symptom onset.

Any symptomatic patient who is under any of the epidemiological factors is put into place of infection control and testing for virus and supportive tests.
According to WHO following human specimen should be collected for viral testing

A. Upper respiratory tract:
   a. Oro-pharyngeal swab
   b. Nasopharyngeal swab
B. Lower respiratory tract:
   a. Sputum
   b. Endotracheal aspirate
   c. Bronchoalveolar lavage – This can only been collected from the mechanically ventilated patients.

All the samples require storage at 4°C. In the laboratory real-time PCR is the only method of testing the material. In this method amplification of the genetic material collected for the specimen by the process of reverse polymerase chain reaction followed by synthesis of double stranded DNA from RNA mold. Probe used on the initial genetic material collected for testing. The vehicle responsible for transportation of the patient has to be disinfected regularly as well as manged with well-protected personnel.

Other supportive tests are the following

A. Complete blood count:
   a. Decreased white blood cell count
   b. Decreased lymphocyte count – it is negative prognostic factor.
B. Blood biochemistry:
   a. Hyperbilirubinemia
   b. Increased lactate dehydrogenase (LDH)
   c. Creatine phosphokinase (CPK)
   d. Myocardial enzymes to exclude cardiac failure.
C. C-reactive protein raised
D. Procalcitonin –Normal
E. D-dimer will be increased and other coagulation disorders are found in critically ill patients.
F. Arterial blood gas analysis – as per requirement.
G. Regular monitoring of chest X-ray to detect any changes.

Management

In case of close contacts as per notice of CDC

a. Don’t panic but don’t go for work outdoor.
b. Detail check up of the health condition and the health check-up record should be sent to the authority
c. Regular check-up by the community doctor
d. In case of appearance of symptoms, like, fever, cough, soreness the person has to attend community health centre for further evaluation and treatment.

In case of possibly infected person following should be recommended:

a. The person should go to designated medical institution for evaluation, diagnosis and treatment.

b. The person should disclose his recent history of travel, residence when he has been in the epidemic areas recently, contact with suggestive respiratory symptoms or suspected CoVID-19 patient and animals.
c. During his visit surgical masks should be worn to protect himself as well as others.

Admission in isolation

a. Most of the suspected patients should be isolated in an isolation centre for protection and regular check-up.
b. Positive but mildly symptomatic patient should be kept in isolation ward for regular check-up.
c. Critically ill positive patients should be admitted in ICU as soon as possible for non-invasive or invasive ventilation.

Transportation of the vehicles: The vehicle responsible for transportation of the patient has to be disinfected regularly as well as manned with well-protected personnel.

Personal protections:

A. Washing of hands with antimicrobial soap and rinsing under running water after any contact with respiratory secretions followed drying with clean towels.
B. Mouth and nose should be covered with surgical or N95 mask, touching of eyes, mouth and nose should be avoided after washing the hands. As the mask can block the carrier of the viruses, aerosol in long distance and droplet in close contact it will prevent the virus entry.
C. Balanced diet, to maintain health and immunity, regular exercise and regular sleep schedule.
D. Windows should be kept open regularly to get fresh and open air.
E. In case of appearance of any symptom, fever, cough doctor should be informed
F. Crowded and enclosed places should be avoided

<table>
<thead>
<tr>
<th>Types</th>
<th>Uses</th>
<th>Filtration efficiency</th>
<th>Number of uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N95 mask without breathing valve or N95 respirator</td>
<td>Respirator effectively filter the particulate matters from the air, effective for airborne respiratory diseases. Valve allows exhale to escape but without allowing small particle to enter. It prevents accumulation of moisture and heat within the mask.</td>
<td>It will block 95% of very small particles of 0.3 μm in size.</td>
<td>Can be reused but has to be discarded when damaged.</td>
</tr>
<tr>
<td>N95 mask with breathing valve</td>
<td></td>
<td>Filteration efficiency is not uniform. It will prevent the entry of particles having 0.5 μm in size. Water-repelling outer layer blocks the droplets from entering the mask.</td>
<td>Can be reused but has to be discarded when damaged.</td>
</tr>
<tr>
<td>Surgical mask</td>
<td>It is used as basic protective gear for medically related professionals. It will protect from droplets containing germs.</td>
<td>It blocks 95% of small particles of 0.3 μm in size.</td>
<td>Single use</td>
</tr>
<tr>
<td>General medical mask</td>
<td>Mask is used for medical procedures, ordinary environment for blocking particles, like, pollen and pathogenic microorganism.</td>
<td>It is not efficient for filtering particles and bacteria.</td>
<td>Single use</td>
</tr>
</tbody>
</table>
Replacement of mask: As every mask has limited protective effect, it should be replaced at regular interval in following cases:

A. Even there is difficulty to breath through the mask.
B. In case of damaged mask
C. If the mask cannot fit snugly to the contour of the face
D. If the mask is contaminated with blood or any secretion
E. After exit from the isolation ward or after contact with the infected person.

There is no guideline regarding the timing of use of N95 mask from WHO but researchers have shown that after 3 day use filtration capability will be reduced up to 94.7%. But due to short supply of N95 mask CDC instructed to use it till it will be visibly damaged or creased or torn.

In case of special population

A. In case of pregnant women professional man should be contacted prior to wearing the mask.
B. In case of patient with cardiac failure or COPD mask may aggravate the illness so they should consult doctor prior to its use.

Following chemicals are sensitive to COVID-19:

A. 75% alcohol
B. Formaldehyde
C. Chloroform
D. Peracetic acid
E. Chlorine containing disinfectants
F. Ultraviolet rays

Home quarantine for a suspected patient

A. Home should be well-ventilated.
B. Number of care-takers should be limited. Care-taker should not have any chronic disease.
C. Family members should be at least 1 meter distant from the patient
D. Nursing mother can continue breast-feeding to her baby.
E. Movement of the patient should be restricted to minimize the shared areas, like, kitchen, bathroom.
F. When staying with the patient properly fitted mask should be worn and not to touch the mask with unclean hands.
G. Hans should be washed every time during contact with the patient, before and after preparing the food, after going to the toilet.
H. Good hygiene of the respiratory tract should be maintained.
I. Direct contact with the human droplets, oral and respiratory secretions and stool.
J. Disposable gloves are required during cleaning of the mouth and respiratory tract and during handling of the feces.

Following life-styles should be maintained during the outbreak of COVID-19:

A. High protein foods including fish, egg, meat, milk, nuts, legumes
B. Fresh fruits and vegetables
C. At least 1500 ml of water per day.
D. Balanced animal and vegetable diet
E. Undernourished, elderly, patients with chronic diseases are recommended to take supplemental commercial nutrition, and this supplement should not be not less than 2100 Kj per day.
F. Never fast during the epidemic of COVID-19.
G. Personal exercise for 1 hour per day.

Hazards of smoking and excessive alcohol intake

A. Smoking increases the nicotine content of the blood leading to transient vasospasm producing hypoxia in the vital organs especially respiratory tract and it will decrease the immunity.
B. Excessive alcohol intake will produce harm to the gastrointestinal tract and liver and thus reducing the immunity.

Supportive therapy with monitoring:

In case of SARI PATIENTS

a. Oxygen therapy should be started at a rate of 5 liter/minute so that it will reach the target SpO2 ≥90% in case of non-pregnant and in case of pregnant it will be ≥92° – 95%.
b. In case children with signs of emergency oxygen therapy should be provided to reach the target SpO2 ≥94% and in case non-emergency situation the target SpO2 should be ≥90%.
c. During this time pulse oximeters, disposable single use oxygen delivery interfaces must be beforehand.
d. In case of SARI without shock adequate intravenous fluid should be administered cautiously to because aggressive administration of fluid may deteriorate oxygenation where there is limited availability of mechanical ventilation.
e. Empirical antibiotics should be started based on clinical diagnosis, local epidemiology, microbial susceptibility data, treatment guidelines. If there is any travel history or exposure to animal influenza virus, neuraminidase inhibitor should also be administered along with the antibiotics. Later on, based on culture susceptibility proper antibiotic should be
f. Administration of corticosteroids: Earlier many systematic review demonstrated that administration of steroids in case of SARS patients there was no survival benefit rather than possible harms, like, diabetes, avascular necrosis, psychosis, delayed viral clearance. But a recent study on MERS patients receiving corticosteroids demonstrated that there was delayed clearance of virus from respiratory tract but there was no mortality due to complications of steroids.
g. Close monitoring of the patients to see any clinical deterioration of the patient, if required emergency supportive care should be provided.

h. In case presence of any co-morbidities in the SARI patients that should be treated along with this emergency therapy.

i. Patient’s party should be communicated beforehand to explain the condition of the patient and time to time follow-up notes also have to be explained.

**Management of ARDS**

a. Hypoxemic respiratory failure in ARDS is mainly due to ventilation-perfusion mismatch or shunt which requires mechanical ventilation as this type of patient has increased work of breathing and hypoxemia in spite of high oxygen flow through face mask or reservoir bag.

b. High flow nasal cannula: If there is no improvement of oxygenation with standard oxygen therapy, then non-invasive ventilation is considered and should be monitored by experienced physician who is capable of endotracheal intubation for 1-2 hours. If there is no improvement in oxygenation and increased work of breathing, then endotracheal intubation followed by mechanical ventilation will be the procedure of choice. Noninvasive ventilation is not recommended in case of hypoxemic respiratory failure or in pandemic viral illness because of the following risks which includes: delayed intubation, large tidal volumes and injurious transpulmonary pressure. Trial with NIV in case of MERS infected patient demonstrated a high failure rate.

c. One person properly trained in endotracheal intubation should be kept in solution ward as because proper care should be taken in case of children, obese and pregnant patients. Pre-oxygenation with 100% FiO2 with any type of mask for 5 minutes followed by rapid sequence intubation will be the procedure of choice.

d. Recommendations in case ARDS are to use low tidal volume (4-8ml/kg of predicted body weight) and lower respiratory pressure (plateau pressure <30 cm of H2O in case of sepsis induced respiratory failure. If pH is 7.30 – 7.45, hypercapnia will be permitted. In case of irritable patients sedation will be required for:

1. Getting the target tidal volume
2. Controlling the respiratory drive.
3. In case of severe respiratory distress and if adequate expertise is in hand, prone ventilation for more than 12 hours is required.
4. Adequate and judicious intravenous fluid should be given in patients with ARDS without tissue perfusion.
5. In ARDS high positive end expiratory pressure (PEEP) is recommended but it requires proper titration because good titration produces less barotrauma and increased number of alveolar recruitments; on the other hand, bad titration may increase ex-expiratory overdistension leading to injury to the lung and increased pulmonary vascular resistance. Related manoeuvre, like, recruitment manoeuvre can be delivered as episodic basis with high continuous positive airway pressure (30 – 40 cm of H2O, progressive incremental increase in PEEP with constant driving pressure or high driving pressure, but risk/benefit ration is similar.

**Management of sepsis**

a. Vasopressor is needed when the criteria given previously in the definition of septic shock. Standard protocol includes empiric wide spectrum antibiotic therapy, adequate fluid administration and vasopressor therapy. For correction of septic shock introduction of central venous catheter or arterial catheter are needed to monitor the parameters.

b. During resuscitation in case of adult, 30 ml/kg of body weight isotonic normal saline in 3 hours and in case of children 20 ml/kg has to be given in bolus followed by 40-6- ml/kg in first hour. But colloid and hypotonic crystalloid solution should not be used.

c. If there is evidence of fluid overloading as evidenced by jugular venous distension, basal crepitation, pulmonary edema and hepatomegaly, fluid administration should be discontinued. Additional fluid can be given in bolus (250 ml – 1000 ml in case of adult and 10 – 20 ml/kg in children) to reach the target of mean arterial pressure of >65 mm of Hg and urine output of >0.5 ml/ml/kg/minute in adult and 1 ml/kg/minute in children.

d. Other indicators of volume responsiveness which can guide the fluid administration are:

1. Passive leg rising,
2. Serial stroke volume measurement with fluid challenges,
3. Variation in systolic pulse pressure,
4. Girth of inferior venacava
5. Stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.
6. If there is persistent hypotension in spite of fluid administration, vasopressor has to be given to reach the target of MAP >65 mm of Hg through large vein, better through central vein or through intraosseous needles.

**Other measures**

If there is any deterioration of oxygenation indicators, excessive activation of inflammatory response, short term glucocorticoids for 3 – 7 days in the form of methyl prednisolone 1 -2 mg/kg/day as because of larger dose and administration of steroids may delay the removal of coronavirus due to immunosuppressive effect. In case pregnant woman it will be better to terminate the pregnancy.

**Prevention of complications**

a. Reduction of duration of mechanical ventilation:

1. Daily assessment of the weaning protocol to observe whether the patient is taking spontaneous breathing.
2. Sedation should be minimised gradually or intermittent sedation.
b. Reduction the incidence of ventilator-associated pneumonia:
   1. In case adolescence and adult oral intubation is preferred.
   2. Head end of the bed should be elevated by 30° to 45°.
   3. Close suction system is required to drain the condensate in the tubing.
   4. For one patient a new ventilator should be used.
   5. Dead moisture exchanger should be changed in case of malfunctioning.
   c. Venous thromboembolism can be prevented by:
      1. Pharmacological prophylaxis –
         • low molecular weight heparin.
         • 500 units heparin subcutaneously.
      2. In case of any contraindication to heparin, intermittent pneumatic compression devices should be used.
   d. Recurrent catheter related infection in the blood can be prevented by:
      1. Sterile introduction of the needle.
      2. Removal of the catheter in case of no-requirement.
   e. Pressure sore can be avoided by:
      1. Frequent change of posture of the patient at every 2 hours.
      2. Provision of air-mattress.
   f. ICU related weakness can be prevented by active mobilization of the patient early in the course of illness.
   g. Stress ulcer can be prevented by:
      1. Provision of early enteral nutrition
      2. Administration of proton pump inhibitors in the patient with risk of bleeding from gastrointestinal tract in following circumstances:
         • Mechanical ventilation for more than 48 hours.
         • Coagulopathy
         • Liver disease
         • Renal replacement therapy
         • High score of organ failure
         • Multiple co-morbidities.

Specific therapy for SARS-CoV-2 virus

There is no specific therapy for this virus till today. But in some cases. Following anti-viral therapy is in the pre-clinical stage. Few areas in India, hydroxychloroquine with ritonavir/lopinavir have been used with some success. But the adverse effects of these drugs may lead to discontinuation of the therapy.

Ritonavir/lopinavir

These drugs can be used in COVID-19 POSITIVE patients having following criteria:

   a. Hypoxia
   b. Hypotension
   c. New organ dysfunction:
      • Increase in creatinine by 50% from the baseline.
      • Reduction of glomerular function rate by more than 25% from the baseline.
      • Urine output to less than 0.5 ml/kg for 6 hours.
      • Reduction Glasgow coma score by 2 or more
      • Any other organ dysfunction.
   d. High risk group:

   • Age ≥60 years.
   • Present of co-morbidities, diabetes, chronic lung disease, chronic kidney disease
   • Immunocompromised patients

Dosage:
   a. Lopinavir/Ritonavir: (200/50) mg – 2 tablets twice daily
   b. If the patient is unable to take oral tablets:
      Lopinavir (400 mg) / ritonavir (100 mg) – 5 ml twice daily
      Hydroxychloroquine 200 mg once/twice daily can be given.
      The adverse effect is QT prolongation.

References

10. Collins AR, Knobler RL, Powell H, Buchmeier MJ. Monoclonal antibodies to murine hepatitis virus-4 (strain JHM) define the viral glycoprotein responsible


