SARS CoV-2 & COVID-19 Pandemic

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Introduction :

COVID-19 was first reported in Wuhan, China, and then it spread worldwide. This new corona virus was named SARS-CoV-2 (severe acute respiratory syndrome corona virus 2) by the International Committee on Taxonomy of Viruses on the basis of phylogenetic analysis. SARS-CoV-2 is thought to be an animal corona virus which jumped a species and then adapted the ability of human-to-human transmission. Because the virus is highly contagious, it is rapidly spreading and is also continuously evolving in the human population. It is a devastating threat to lives and livelihood globally. There are continuous new discoveries in everything related to this disease starting from virus itself to new syndromes, therapies and vaccines. Results of the whole-genome sequencing showed that the causative agent was a novel coronavirus. This virus is the seventh member of the corona virus family to infect humans.[1]

Time line of Covid-19 :

There was first report and subsequent outbreak of a cluster of human pneumonia cases in Wuhan City, China, since late December 2019. The symptoms of these patients included fever, malaise, dry cough, and dyspnea and was diagnosed as viral pneumonia. Initially, the disease was called Wuhan pneumonia because of the area and pneumonia symptoms.

31 Dec 2019: Municipal Health Commission of Wuhan, China reported a cluster of cases resembling viral pneumonia in Wuhan, Hubei Province of China which was later on identified as novel coronavirus.

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5 January 2020: WHO published the first Disease Outbreak News regarding the new virus.

12 January 2020: China publicly shared the genetic sequence of COVID-19.

14 January 2020: WHO's technical lead for the response responded that there may have been limited cases of human-to-human transmission of the coronavirus (Amongst 41 confirmed cases).

January 2020: WHO (The World Health Organization) temporarily named the new virus 2019 novel coronavirus (2019-nCoV) and then officially named the disease caused by the virus as coronavirus disease 2019 (COVID-19).

February 2020: The ICTV (International Committee on Taxonomy of Viruses) officially named the virus as SARS-CoV-2 based on phylogeny, taxonomy and established practice.

March 2020: WHO declared that Covid 19 was Pandemic.

Status as of November 17, 2020

- Total Cases Confirmed Globally: 55,243,538
- Total Deaths Worldwide: 1,330,930
- Number of countries with cases: 214

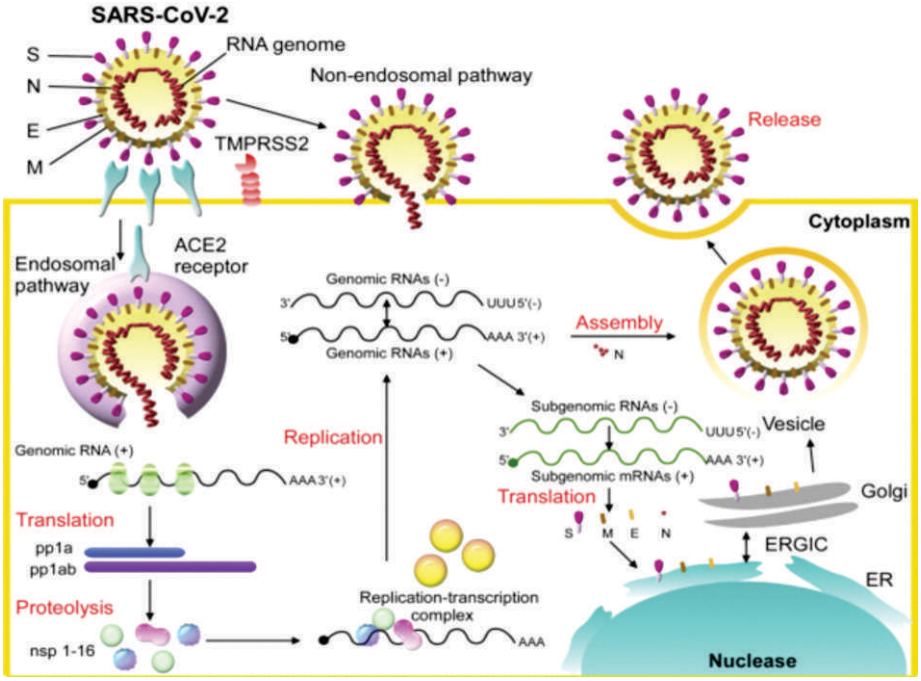
Virology – morphology, gene structure and replication [1] :

SARS-CoV-2 virus is an enveloped spherical particle around 120 nm in diameter and it contains a positive-sense single-stranded RNA genome. It belongs to the subfamily Coronavirinae from family Coronavirdiae belonging to order Nidovirales. It is classified in a beta-coronavirus category. The closest RNA sequence similarity is to two of the bat coronaviruses, and the bats are believed to be the primary source.

The human coronavirus (HCoV) strains HCoV-NL63, HCoV-229E, HCoV-HKU1, and HCoV-OC43 mostly cause mild, self-limiting upper respiratory tract infections, like the common cold. However, SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe acute respiratory syndrome and may be responsible for life threatening disease.

This corona virus transcribes nine subgenomic RNAs, and its genome is consisting a 5 untranslated region including a 5 leader sequence and an open reading frame (ORF) 1a/ab which encodes NSP (nonstructural proteins) for replication, It also contains four structural proteins called spike (S), envelope (E), membrane (M) and nucleocapsid (N) and also some accessory proteins named ORF 3a, 7a/b,6 and 8; and a 3 untranslated region .Then the spike glycoprotein of SARS-CoV-2 binds to ACE2 (angiotensin-converting enzyme 2) receptor in humans and it is also dependent on S protein priming done by the serine protease TMPRSS2. The spike protein is cleaved by host proteases into the S1 subunit which is responsible for receptor recognition and S2 subunit, which is responsible for membrane fusion. S1 is again divided into an N-terminal domain (NTD) and a C-terminal domain (CTD). The S1 CTD of SARS-CoV-2, shows strong affinity for hACE2 (human ACE2) .The receptor-binding domain (RBD) within SARS-CoV-2 CTD is the main region that interacts with the hACE2 receptor. The life cycle of SARS-CoV-2 in host cells begins when spike protein and hACE2 receptor binds to one another. The conformational change which occurs when S protein binds with receptor will facilitate viral envelope fusion with the cell membrane via the endosomal pathway. The viral RNA genome is then released into the cytoplasm which is converted into viral replicase polyproteins which are known as pp1a and 1 ab, which is divided into small products by virus-encoded proteinases. This polymerase reproduces a series of subgenomic messenger RNAs by discontinuous transcription and which are then converted into viral structural proteins. The S, M and E proteins enter the ER (endoplasmic reticulum) and Golgi apparatus, and finally N protein is combined with the positive-stranded genomic RNA and thus forms a nucleoprotein complex. This Nucleoprotein complex and the structural proteins are assembled with the viral envelope at the ER–Golgi intermediate compartment. The newly formed viral particles are then released from the infected cell.

Figure 1 : Morphology & Replication of SARS-CoV-2



Amino acid changes in the spike protein of SARS-CoV-2 isolates were monitored in a large sequence database and they identified a D614G (glycine for aspartic acid) substitution that became the dominant polymorphism all over the world over time. **The emergence of G614 (called G 614 mutation) as the dominant variant may be related to high infectivity. Recently identified mutation on spike protein called N501Y is creating havoc in UK as its transmissibility is supposedly 70 % more.**

The supposed life cycle of SARS-CoV-2 [1]:

Bats are probable reservoir hosts for SARS-CoV-2; however, whether Bat-CoV RaTG13 directly jumped to humans or was transmitted thorough intermediate hosts to facilitate animal-to-human transmission remains unproven. It has been suggested that pangolins might be the intermediate hosts between bats and humans because pangolin coronavirus is similar to SARS-CoV-2.

In a phylogenetic network analysis of 160 complete human SARS-Cov-2 genomes, scientists found three main variants which were differentiated by amino acid changes, which were named A, B, and C. A was the ancestral type according to the bat outgroups coronavirus. The A and C types were found in huge proportions, in Europeans and Americans while the B type was the most common type in East Asia.[2]

Pathogenesis :

Endothelial injury – researchers have found evidence of direct invasion of endothelial cells by the SARS-CoV-2 virus, leading to cell injury. It is postulated that endothelial injury, endothelial exocytosis, microvascular inflammation and/or endotheliitis play an important role in the pathogenesis of ARDS and MODS in patients with severe COVID-19.

There is also a suggested a role of neutrophil extracellular traps (NETs), which is a form of decondensed chromatin that is extruded by dead or dying neutrophils, in the prothrombotic state in COVID-19

Intravascular catheters and cytokines (e.g, interleukin [IL]-6) and other acute phase reactants may also produce endothelial injury. Complement-mediated endothelial injury has been suggested as a possibility.

Stasis – Immobilization can cause stasis of blood flow in all critically ill hospitalized patients.

Hypercoagulable state-due to circulating prothrombotic factors- Elevated factor VIII , circulating prothrombotic micro particles, Elevated fibrinogen, hyper viscosity, neutrophil extracellular traps (NETs), lupus anticoagulant. LA-positivity is associated with thrombosis in patients with COVID-19. Very elevated levels of D-dimer have been observed which correlate with illness severity.

VWF antigen is also greatly increased and is consistent with endothelial injury. Some studies found complete lack of clot lysis, known fibrinolysis shutdown and that is usually associated with a greater increase in kidney failure and thromboembolic events. This has been called thromboinflammation or COVID-19-associated co-agulopathy .

Transmission :

Direct person-to-person respiratory transmission is the primary mode of transmission of SARS-CoV-2. It occurs mainly through close contact (within six feet or two meters) via respiratory droplets. Virus which is released in the respiratory secretions when an infected person talks, coughs or sneezes can infect another person if it is inhaled or makes direct contact with the mucous membranes. Infection may also occur if a person's hands are contaminated by droplets or by touching contaminated surfaces and when they touch their eyes, nose, or mouth with their hands. Contaminated surfaces are not thought to be a major route of transmission for Covid-19 as per WHO.

SARS-CoV-2 can also be transmitted longer distances through the airborne route (through inhalation of particles smaller than droplets which remain in the air over some time and distance), but the extent to which

this mode of transmission is contributing to the pandemic is controversial. Some reports of SARS-CoV-2 outbreaks (e.g., in a restaurant, on a bus) have highlighted the possibility for longer distance airborne transmission in poorly ventilated enclosed spaces while speaking, coughing or sneezing. Viral RNA was also discovered in air samples of hospital rooms of COVID-19 patients and in ventilation systems in some studies.

After few reports of clusters of Covid-19 cases in a dense urban community and in a residential building with poor sanitation, the possibility of transmission through aerosolization of virus from sewage drainage was suggested. As per WHO, transmission through the fecal-oral route does not look like an important factor in the spread of Covid-19 infection.

Infected individuals are more likely to be contagious in the earlier period of illness, when viral RNA levels from respiratory specimens are the highest. As per studies infectivity starts 2.3 days before symptom onset, highest at 0.7 days before symptom onset and decreases within seven days.

In a review of 28 studies, the median duration of viral RNA detection in respiratory specimens was 18 days after the onset of symptoms; in some patients, viral RNA was detected from the respiratory tract several months after the initial infection which however does not suggests the presence of infectious virus, and there seems to be a threshold of viral RNA level below which infectiousness of the virus is unlikely. In a study of patients with mild COVID-19, virus was not detected from respiratory specimens when the viral RNA level was <106 copies / mL. High viral RNA concentrations are reflected by lower numbers of reverse transcriptase polymerase chain reaction (RT-PCR) amplification cycles needed for detection. Depending on the study, the cycle threshold (Ct) for specimen culture positivity may vary from <24 to ≥32.

Transmission of SARS-CoV-2 from individuals with infection but no symptoms (including those who later developed symptoms and thus were considered pre-symptomatic) has been well documented.

Immunity following infection :

After an infection with SARS-CoV-2, most of the patients develop detectable serum antibodies to the receptor-binding domain of the spike protein and neutralizing activity. The amount of antibody response may be associated with severity of disease. Patients with mild infection may not have detectable neutralizing antibodies. The duration of neutralizing antibody following infection is not certain, as they decrease gradually over several months.

Studies have found SARS-CoV-2-specific CD4 and CD8 T cell responses in patients who recovered from COVID-19 and it was also seen in persons who had received an investigational SARS-CoV-2 vaccine, which suggest the possible long lasting T cell immune response. Over all, the short-term risk of reinfection appears low. However, sporadic cases of reinfection have been documented.

Risk factors for severity [3]:

Life style risk factors- Smoking, a higher body mass index (obesity) and a longer waiting time to hospital admission.

Demographic risk factors- Higher age, male gender, post menopause status and higher age in females. Some publications specify the age for increased risk as > 64 or > 65 years & pregnancy.

The pre-existing comorbidities- Hypertension and diabetes followed by cardiovascular disease, cerebrovascular disease , chronic obstructive pulmonary disease , chronic renal disease or tuberculosis, cancer, immunocompromised state, sickle cell disease, liver disease, cystic fibrosis, pulmonary fibrosis, Thalesemia etc.[4]

The co-morbidities developed during Covid-19 having significant impact on disease severity they are - organ failure , immunological dysfunction, acute liver injury, hypoproteinemia, Acute Respiratory Distress Syndrome (ARDS), severe pneumonia, uncontrolled inflammation response and hypercoagulable state.

The common investigation parameter associated with increased severity are: Decreased lymphocytes, increased C-reactive protein (CRP), increased d-dimer level, increased leucocytes, increased neutrophil count, low oxygen saturation, increased CT severity score, increased interleukin 6 (IL-6) level, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased blood urea nitrogen (BUN), decreased thrombocytes, decreased blood sodium or decreased erythrocytes count. Over and above the factors already mentioned, the symptoms fever (> 38.5°C) and dyspnea are also associated with severe disease progression.

As per WHO statement released on 14th December, health workers account for an around 3% of the world's population, but they account for 14% of all infections with COVID-19.That is an important risk factor.

Clinical manifestations

One of the most important and puzzling features of COVID-19 disease which is never seen till this date is the wide spectrum of clinical manifestations, complications and outcomes, which ranges from asymptomatic cases to various degrees of organ dysfunction to death.

Most common symptoms: Fever, Dry cough, Tiredness

Less common symptoms: Aches and pains, Sore throat, Diarrhoea, Conjunctivitis, Headache

Loss of taste or smell, Rash on skin, or cyanosis

Serious symptoms: Dyspnea, Chest pain or pressure, Loss of speech or movement

Multisystem inflammatory syndrome in children (MIS-C)

Children are less affected by COVID-19 as compared to adults. In children, COVID-19 is usually mild. However, in rare cases, children can be severely affected, and clinical manifestations are different then in adults. In April 2020, there were first reports from the U.K of a presentation in children which was similar to incomplete Kawasaki disease (KD) or toxic shock syndrome. It was thought that this syndrome may be the result of an abnormal immune response to the virus and is similar to Kawasaki disease (KD), macrophage activation syndrome (MAS) and cytokine release syndrome.

Clinical manifestations of MIS-C are: Persistent fever (four to six days) – 100 %, Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) – 60 %, Rash – 45 to 76%, Conjunctivitis – 30 to 81%, Mucous membrane involvement – 27 to 76%, headache, lethargy, confusion – 29 to 58%, Respiratory symptoms – 21 to 65 %, Sore throat – 10 to 16%, Myalgia – 8 to 17%, Swollen hands/feet – 9 to 16 %, Lymphadenopathy – 6 to 16 %.

Complications in patients with COVID-19

- Pneumonia
- Hypoxemic respiratory failure/acute respiratory distress syndrome (ARDS)
- Diffuse alveolar damage
- Secondary bacterial infections
- Sepsis and septic shock, DIC
- Cardiomyopathy
- Cardiac injury
- Sudden cardiac death
- Thromboembolism
- Gastrointestinal bleeding
- Arrhythmia
- Acute kidney injury
- Liver dysfunction/Acute liver injury
- Multiorgan failure
- Critical illness polyneuropathy / myopathy
- Secondary hemophagocytic lymphohistocytosis (SHLH)
- Rhabdomyolysis
- Aspergillosis
- Pancreatic injury
- Neurologic complications (encephalopathy, meningoencephalitis, GB syndrome etc).

- Subacute thyroditis
- Immune thrombocytopenia
- Autoimmune hemolytic anaemia

Post Covid symptoms or Long Covid [7]

Most patients recover completely within few weeks but some patients have persistent symptoms for weeks or months, even those with mild illness. The condition is defined when, symptoms and signs which develop during or after Covid infection and are consistent with COVID-19 infection but continue for more than 12 weeks, and they are not explained by any alternative diagnosis. Ongoing symptomatic COVID-19 is another entity and is defined as symptoms and signs lasting for 4 weeks to 12 weeks.

Symptoms of post Covid illness include: fatigue, persistent cough, dyspnea, joint pain, chest pain, myalgia, palpitation, persistent loss of taste or smell, visual problems, hearing loss, mood disorder, depression, anxiety, post traumatic stress disorder, cognitive problems like impaired memory and concentration or sleep problems, tremors, dizziness hair loss, rash, chronic fatigue syndrome. Increased tendency for infection like mucormycosis is observed in our country in patients with diabetes and sometimes nondiabetics recovering from Covid-19. There may still be newer symptoms likely to be discovered.

Post Covid symptoms may also be due to organ damage during infection:

- **Heart :** Imaging tests done after months of recovery from COVID-19 have shown lasting damage to the heart muscle, even in those who suffered only mild COVID-19 disease. This may increase the risk of heart failure or other complications in the future.
- **Lungs :** The pneumonia commonly associated with COVID-19 can cause long term damage to alveoli in the lungs. The resulting fibrosis can lead to long-term dyspnea and other complications.
- **Brain.** : Even in young people, COVID-19 can cause seizures, strokes and GB (Guillain-Barre) syndrome. COVID-19 has been thought to be associated with increased risk of developing Alzheimer's disease and Parkinsonism.

Laboratory diagnosis:

Detection of SARS-CoV-2 RNA by RT PCR (reverse transcription polymerase chain reaction) is required. Nasopharyngeal samples are better as compared to the throat samples. It is the recommended gold standard test. Most assays detect SARS-CoV- 2 specific genes such as S, N (N1, N2), ORF 1ab and RdRp. Lower respiratory samples may have better yield though. These tests have high specificity but their sensitivity ranges from 60-90 %. If the initial test is negative, but there is a strong clinical suspicion, it is advisable to do repeat test in 24-48 hrs when the result is likely to be positive .The limit of detection of most of these tests is 100-250 RNA copies / ml and an infected person usually has 105 – 106 copies / ml in the nasopharynx.[5]

Rapid antigen based assay has received ICMR approval and it is a point of care test recommended for use in containment zones and healthcare settings. This test has excellent specificity. So if it is positive, confirmation with an RTPCR test is not needed. But a negative test result will need to be confirmed. The results are available by 30 minutes.

Covid-19 antibody test (serological test)- It identifies individuals who have been previously infected or cases who present late in the disease course, for determining disease prevalence in particular area, to identify convalescent plasma donors and also to evaluate immune response to candidate vaccines. Antibody based assays require careful and judicious interpretation.

Treatment of Covid-19[6]

Ministry of health and Family welfare Govt.of india has guidelines for each category of patients

Infection prevention control (IPC) is extremely important and integral part of management of patients and should be started at the point of entry of the patient to hospital and to be continued at every stage.

Mild disease

Clinical features-patients with uncomplicated upper respiratory infections with mild symptoms like fever, nasal congestion, sore throat, headache and malaise without breathlessness.

Treatment: Isolation, look for co-morbidities. Patient is to be followed up daily for vitals, temperature, and SpO_2 (Oxygen saturation); immediate hospitalization if symptoms worsen. Paracetamol for fever and pain, anti-tussives for cough; adequate nutrition and appropriate hydration; tab. Hydroxychloroquine (HCQ) may be considered for those having high risk features for severe disease but to be avoided in cardiac disease or prolonged QT on ECG.

Moderate disease-(pneumonia with no signs of severe disease)

Clinical features:

Adults- presence of clinical features of dyspnea / hypoxia, fever, cough, SpO_2<94% on room air, respiratory rate more or equal to 24/minute. Children - Criteria is same as adults for older children. Fast breathing will be considered if, in breaths/min is 60 in children less than 2 months; ≥50 in children 2–11 months; & is ≥ 40 in children 1–5years of age.

Clinical Management of Moderate cases:

- Paracetamol for fever and pain, anti-tussives for cough can be continued.
- Adequate hydration
- Oxygen Support - Target SpO_2: 92-96% (88-92% in patients with COPD)
- Administer oxygen (nasal prongs, mask, or masks with reservoir bag) depending upon the increasing requirement of oxygen therapy.
- Awake proning may be used as a rescue therapy in selected patients. Protocols recommends patients to be kept for 30–120 minutes in prone position, followed by 30–120 minutes in left lateral position , right lateral position, and upright sitting position.
- Daily 12-lead ECG.
- Anticoagulation-Prophylactic dose of UFH or LMWH (Enoxaparin 40 mg per day SC).Contraindications: Active bleeding, End stage renal disease(unfractionated heparin can be given) and emergency surgery.
- Corticosteroids- IV methylprednisolone 0.5 to 1 mg/kg or Dexamethasone 0.1 to 0.2 mg/kg for 3 days (it should be preferably given within 48 hours of admission or if O2 requirement is increasing and also if inflammatory markers are increased). Duration is to be reviewed as per clinical response.
- Remdesivir (under EUA) may be considered as investigational therapy. Contra-indicatations for Remdesivir are- AST/ALT > 5 times Upper limit of normal , pregnancy or lactating females and children below 12 years of age, Severe renal impairment (i.e., eGFR < 30ml/min/m2 or need for hemodialysis). Dose: 200 mg IV on first day followed by 100 mg IV daily for 4 days (total 5 days)
- Convalescent Plasma is approved for off label use. Dose ranges from 4 to 13 ml/kg (usual dose is 200 ml single dose given slowly over not less than 2 hour) is given in properly selected patients.
- Tocilizumab - can be given to patients with moderate disease with progressively increasing oxygen requirements and in patients on ventilator and those who are not improving despite use of steroids. Long term safety data is unknown. Presence of raised inflammatory markers (e.g., CRP, Ferritin, IL-6) is very important factor to consider for its use. Patients should be carefully

monitored after Tocilizumab therapy for secondary infections and neutropenia. It is contraindicated in PLHIV , those with active systemic bacterial/fungal infections, active hepatitis, tuberculosis, ANC < 2000/ml and platelet count < 1,00,000/mm. Dose: 8mg/kg to be given slowly in 100 ml NS over 1 hour (maximum 800 mg at one time); second dose may be given after 12 to 24 hours if needed.

- Control of co-morbid conditions.
- Follow up CRP, D-dimer & Ferritin every 48-72 hourly. CBC with differential count, absolute lymphocyte count, RFT/LFT to be done daily. Monitor for hemodynamic instability or increase in oxygen requirement.
- Empiric antibiotic therapy for secondary bacterial infection as per local antibiogram and guidelines.

Severe disease (severe pneumonia)

Clinical features:

Adolescent or adult: Clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO_2<90% on room air.

Child with cough or dyspnea, plus at least one of the following: central cyanosis orSpO_2<90%; severe respiratory distress (e.g. grunting, chest in-drawing); signs of pneumonia with any of the following danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present.

Treatment of severe cases:

- Symptomatic treatment with paracetamol and antitussives is to be continued.
- Oxygenation: Give oxygen therapy immediately to patients with Severe Covid and those who have respiratory distress, hypoxaemia, or shock: Initiate it at 5 L/min and titrate flow rates to reach SpO_2 levels $\geq$90% in non-pregnant $\geq$92-96% in pregnant patients. Children with emergency signs like severe respiratory distress, obstructed or absent breathing, central cyanosis, coma, shock, or convulsions should receive oxygen therapy.
- Use fluid management carefully in patients with severe covid particularly if there is no evidence of shock.
- Anticoagulation: same as moderate case.
- Corticosteroids: IV Methylprednisolone 1-2 mg/kg or Dexamethasone 0.2-0.4 mg/kg for 5-7 days.
- Tocilizumab therapy may be considered.

Adult respiratory distress syndrome (ARDS)

Clinical features

Onset: new or worsening respiratory symptoms within one week of known clinical insult. Chest imaging (Chest X ray and portable bed side lung ultrasound) showing bilateral opacities which are not fully explained by effusions, presence of lobar or lung collapse, or nodules, respiratory failure not fully explained by cardiac failure or fluid overload. It is better to do echocardiography to exclude hydrostatic cause of infiltrates/ oedema if no risk factor present.

Oxygenation impairment in adults:

Mild ARDS: 200 mmHg < PaO_2/FiO_2 $\leq$300 mmHg (with PEEP or CPAP $\geq$5 cm H_2O)

Moderate ARDS: 100 mmHg < PaO_2/FiO_2 $\leq$200 mmHg with PEEP$\geq$5 cm H_2O)

Severe ARDS: PaO_2/FiO_2 $\leq$ 100 mmHg with PEEP $\geq$5 cm H_2O)

Treatment:

- Lung protective ventilation strategy by ARDS net protocol
- High –Flow Nasal cannula oxygenation (HFNO)
- NIV: The settings should be -PS 5-15 cmH_2O which is adjusted to tidal volume of 5-7 ml/kg and PEEP should be kept at 5-10 cm H_2O and FiO_2

should be 0.5 -1.0 and titrated to target SpO_2> 94%.However If the parameters do not improve or get worse within 1 to 2 hours, tracheal intubation and invasive mechanical ventilation should be used without delay.

- Mechanical ventilation should be started using lower tidal volumes and lower inspiratory pressures (plateau pressure <30 cmH_2O) and patient needs to be under expert care for proper monitoring.
- In settings with access to expertise in extracorporeal life support (ECLS), patients can be referred for treatment of refractory hypoxemia if persistent despite lung protective ventilation.

Sepsis

Adults: Sudden life-threatening organ dysfunction which is caused by a dys-regulated immune response to suspected or proven infection.

Signs of organ dysfunction are dyspnea, altered consciousness, low oxygen saturation, reduced urine output, tachycardia, feeble pulse, low BP, cold extremities, mottling of skin, or evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or raised bilirubin on investigation.

Children: Presence of infection and ≥2 age based SIRS (Systemic Inflammatory Response Syndrome) criteria.

Septic shock

Adults: hypotension is not improving despite volume resuscitation, requiring vasopressors to maintain Mean Arterial Pressure 65 mmHg and serum lactate level > 2 mmol/L

Children: any hypotension (SBP<5th centile or >2 SD below normal for age) or 2-3 of the following: altered mental state; bradycardia or tachycardia ,capillary refill is more than 2 seconds or feeble pulse; tachypnea, cool or mottled skin or purpuric or petechial rash; high lactate; reduced urine output ; hyper or hypothermia.

Septic shock is to be managed as per standard protocols.

The future prospects in management of Covid-19 :

On the international front, antibody bamlanivimab was granted Emergency Use Authorization (EUA) by the US FDA in November and antibody cocktail REGN-COV2 for EUA was approved later on in November. EUA is also granted to Casirivimab and imdevimab combination. These all still needs larger trials. Available data on these antibodies suggest that they can reduce the need for hospitalization in high-risk patients, and they may have potential for PEP (post-exposure prophylaxis). Both of these drugs are not recommended for use in hospitalized patients. So availability of these antibodies adds to recent developments of medicines which can help reduce mortality of the dreaded disease. Anakinra, which is a recombinant soluble receptor antagonist of IL-1 and IL-1, has been used in certain trials in patients with signs of sHLH due to covid 19 and it reduced mortality. Investigators are also researching oral antivirals, inhaled antiviral therapy and possibility of using interferon therapy for treating excess inflammation of severe Covid 19.

Vaccines for Covid-19:

There are four different types of vaccines undergoing clinical trials: whole virus (Inactivated), Nucleic acid (Plasmid DNA / mRNA), protein subunit, viral vector (e.g. non pathogenic adenovirus).

As on December 2020, there are 40 Covid-19 vaccines undergoing phase1 trial, 17 are in phase 2 trial,15 have progressed to phase 3 trials, 5 vaccines are already in early or limited use, 2 mRNA ones are approved and 1 is abandoned. Almost 85 vaccines are in preclinical trial. [9]

End of pandemic

Before we hope for the end of pandemic, we need to consider the following points. [10]

1) Vaccine age restrictions has raised the coverage requirements for achieving herd immunity .

The two MRNA vaccines mentioned above are indicated first for use in adults. It is not certain when its use in children will be indicated. So there is no clarity regarding its impact on transmission.

2) Unclear impact of vaccines on transmission.

We have data on whether people who are vaccinated are less likely to get sick with COVID-19 (and less likely to get severe disease), but we won't have data on how likely they are to transmit to others.

3) Wide variations in local sero-prevalence suggest the heterogeneous paths to herd immunity.

4) Manufacturing and supply issues may be a problem.

5) Potentially shorter duration of immunity could prolong the path to the end.

6) Mutation of the virus and its adverse effect on pandemic if any remains to be seen.

As per researchers opinion, 3rd quarter or 4th quarter of 2021 are more likely to see herd immunity in the United States even with vaccination. We are not sure when will it be for India but hopefully it will be the same, if not by mass vaccination, may be by herd immunity by natural infection. Of course if it is earlier, it is better and we can surely hope for the same. We still don't know if the world can ever go back to the pre Covid era and how much time it will take to come out of the dreadful effect on many fronts.

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