FEVER FOUNDATION

FEVER

A CONCEPT ANALYSIS

A HANDBOOK FOR COVID WARRIORS

Compilation of articles from

FeFCon 2020 VIRTUAL CONFERENCE

MICRO KNOWLEDGE ACADEMY

FEVER FOUNDATION

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A CONCEPT ANALYSIS

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FOREWORD

The vast majority of fevers are associated with self-limited infections, most commonly of a viral origin, where the cause of the fever is easily identified. The decision to reduce fever with antipyretics assumes that there is no diagnostic benefit of allowing the fever to persist. However, there are rare clinical situations in which observation of the pattern of fever can be helpful diagnostically.

The vast majority of fevers are associated with self-limited infections, most commonly of a viral origin, where the cause of the fever is easily identified. The decision to reduce fever with antipyretics assumes that there is no diagnostic benefit of allowing the fever to persist.

Recognizing symptom patterns can provide crucial clues and, thus, lead to the initiation of targeted specific diagnostic tests and therapies.

There is some debate as to whether fever should be routinely treated. However, people with a high fever generally feel much better when the fever is treated.

Fever can be tricky in older people because the body may not respond the way it would in younger people.

The ability to develop fever in older adults is impaired, and baseline temperature in older adults is lower than in younger adults. Thus, older adult patients with severe infections may only display a modest fever.

This fever book provides the comprehensive information about the fever, its approach and management.

Dr. Maiya M MBBS (Mys), FRCP (lond), FRCP (Edin), FRCP (Glasg), FICP (Ind), FICC (Ind)
Chief patron, Fever Foundation of India, Bangalore
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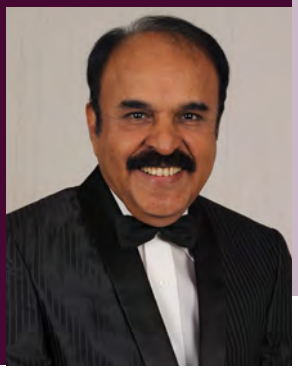
FOREWORD



Fever is one of the body's most effective ways of fighting infection. Fever is a prominent feature of disease since antiquity. It is the balance in the interactions between pyrogens and cyrogens that determine the severity and duration of the febrile response to any immune challenge.

In view of its integral role in the pathogenesis of diseases, fever will remain a cardinal manifestation of old, new and emerging diseases, whether infectious and non-infectious disease. It is therefore imperative for clinicians to continue to harness and expand knowledge gained so far in the understanding of the febrile response in order to improve on the diagnosis, prevention and management of the numerous diseases characterised by fever.

Optimal management of fever is contingent on meticulous patient assessment, with implementation of appropriate treatment interventions as befits patient-determined goals of care. Treatment options include antipyretic therapy and primary approaches targeted at contributing etiologies and pathophysiologic mechanisms.

This fever book is a valuable for the practising physicians to overcome the challenges in fever management in day to day practice.

I hope this book helps in giving insight of fever in normal and special circumstances.

Dr. A. Muruganathan
Chairman- Fever Foundation CME Committee
Governor – American College of Physicians
Past Dean – Indian Collegeof Physicians of India
Past President – Association of Physicians of India
Past president- Hypertension Society of India

FOREWORD

Fever in children is a common concern for parents and one of the most frequent presenting complaints. Although the incidence of serious infections has decreased after the introduction of conjugate vaccines, fever remains a major cause of laboratory investigation and hospital admissions.

Fever plays a physiologic role in response to infection, inhibiting bacterial growth and viral replication, and enhancing the immune response.

Fever itself is not dangerous, antipyretic treatment should be reserved for distressed children, aiming at improving the child's wellbeing rather than achieving normothermia. Antipyretic treatment has not been shown to prevent recurrence of febrile seizures and should therefore not be recommended for this purpose.

Appropriate counselling on the management of fever begins by helping parents understand that fever, in and of itself, is not known to endanger a generally healthy child.

Response to antipyretics cannot predict the severity of the underlying illness, since children with bacterial and viral illnesses have a similar response to antipyretics.

A primary goal of treating the febrile child should be to improve the child's overall comfort. The desire to improve the overall comfort of the febrile child must be balanced against the desire to simply lower the body temperature.

Pediatricians should focus instead on monitoring for signs/symptoms of serious illness, improving the child's comfort by maintaining hydration, and educating parents on the appropriate use of antipyretics.

The Fever Foundation provides scientific data on various aspects of fever for better understanding, care of the child.

This book provides the updates on the latest advances in diagnosis and management of fever in children.

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PROLOGUE

Fever Foundation is an independent, non commercial foundation supporting the educational/ academic activities to address the unmet needs in fever management. The foundation is committed to conceptualise, invigorate programs and develop scientific initiatives aimed at providing evidence based updates to health care professsionals.

The second Annual National conference of Fever foundation, FeFCon 2019 was held on 16th and 17th November at Hotel Shangri -La, Bengaluru. Mind opening presentations by highly esteemed and renowned speakers were delivered in the two days academic feast.

This book is the brief capture of important sessions on fever and its management which can be of great help in day to day practice.

Happy Reading,

Dr. Manjula S
Organizing Secretary,
FeFCon 2019

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COVID 19: AIIMS experiences

Dr. (Prof) Randeep Guleria
Director, AIIMS New Delhi

"Humanity has but three greatest enemies: fever, famine and war: of these by far the greater, by far the most terrible is fever" -Sir William Osler, MD 1896

Introduction

SARS-CoV-2 virus and COVID disease were unknown before the outbreak began in Wuhan, China in December 2019.[1] The disease has emerged as the major public health burden in the world, with morbidity and mortality of global community increasing day by day.[2] The clinical profile of the disease comprises of both symptomatic and asymptomatic presentations, mild to moderate illness, severe illness (severe pneumonia), severe complicated illness (ARDS, sepsis), and atypical cardiac and neurological presentations. The All India Institute of Medical Sciences, New Delhi has been extensively involved in managing patients, framing guidelines, policies and conducting research for effective management of COVID-19.[3] The present review focuses how the AIIMS frontline workers and management has risen up to the situation to tackle the pandemic effectively.

Pathophysiology of COVID-19

COVID-19 can have diverse clinical presentations comprising of cytotoxic effects, dysregulation, endothelial damage, and cytokine release syndrome. SARS-CoV-2 enters the host cells through interaction of its spike protein with the entry receptor ACE2. Type II transmembrane protease TMPRSS2 activates the influenza virus protein for membrane fusion.[4] The proposed mechanisms for COVID-19 infection include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as

a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα.[5]

Case definitions

Majority of the patients are having febrile illness and possibly associated respiratory disease. The case definitions put forth by WHO are briefed below:[6]

Suspect case

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID -19 disease during the 14 days prior to symptom onset.

OR

A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID -19 case in the last 14 days prior to symptom onset.

OR

A patient with severe acute respiratory illness (fever and at least one signs/symptom of respiratory disease, e.g., cough, shortness of breath; and requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A suspect case or whom testing for the COVID 19 virus is inconclusive.

OR

A suspect case for whom testing could not be performed for any reason.

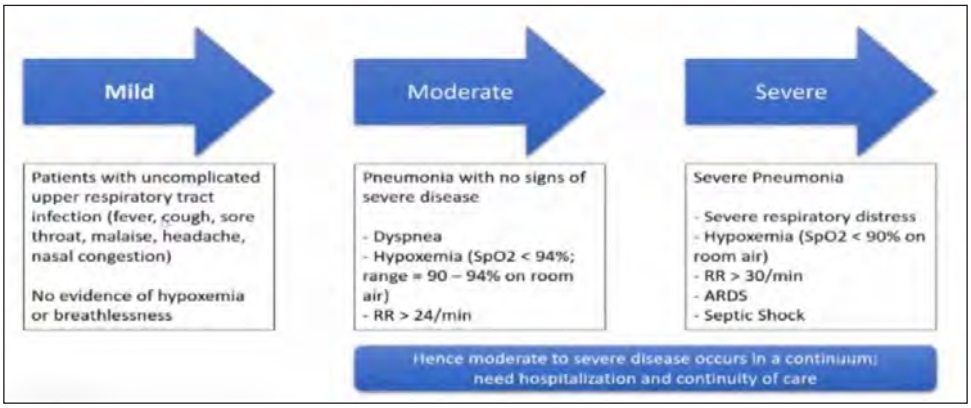
Confirmed case

A person with laboratory confirmation of COVID -19 infection, irrespective of clinical signs and symptoms.

Classification of COVID-19

Classification of COVID based on the signs and symptoms on presentation are depicted in figure 2.

Fig.2: Classification of COVID-19

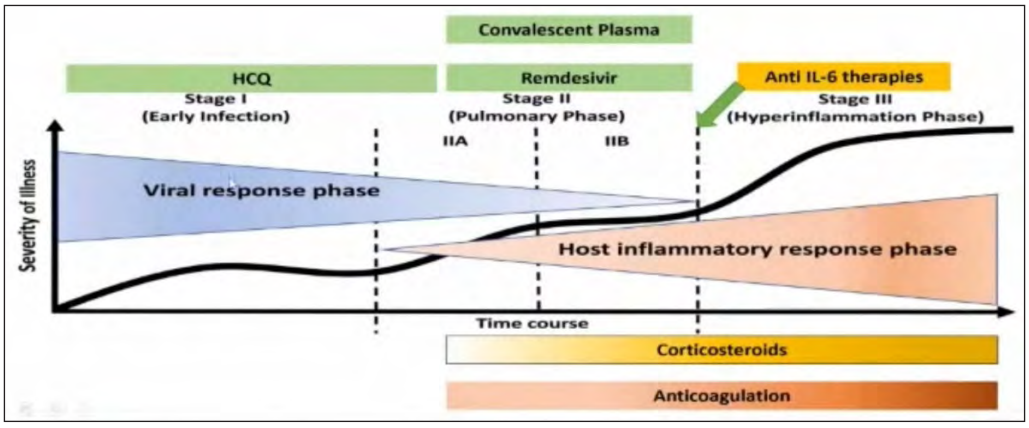


Disease course and treatment

During the early stages of the disease, majority of the subjects present with febrile illness. They may have only viremia, which tends to reduce within 7-10 days of disease onset.[7] About 15-20% of the respiratory involvement leads to hypoxemia and <5% of the cases develop cytokine release syndrome or hyperinflammation phase. In stage 2, remdesivir, steroids, anticoagulants and possibly convalescent plasma are the preferred treatment options. In stage 3, anti-IL-6 therapies can be used (Fig.3).[7]

Predominant care for hospitalized patients comprises of supportive therapy with antibiotics, antipyretics, hydration along with oxygen therapy for hypoxemic patients, antivirals (not very effective), anticoagulants, and anti-inflammatory drugs to patients with cytokine release syndrome.

Fig. 3: Disease course and treatment



Role of AIIMS in COVID management

AIIMS, Delhi is playing a paramount role in conferring effective treatment, preventing disease transmission and providing overall guidance to clinicians across the country. In March 2020, AIIMS has released guidelines on clinical management of COVID, which are intended for clinicians caring for hospitalized adults and pediatric subjects.[8] Many faculties of AIIMS are involved in guiding COVID national task force. An empowered group has been formed in collaboration with Prime Minister's office to develop COVID management strategies for the country. The author is currently chairing the clinical research group of ICMR, to oversee the COVID-related research activities.

So far, 163,082 COVID-suspected patients attended the OPD facility and nearly 9464 patients were treated till now. Evaluation of the age-wise distribution of 4000 patients admitted during the initial phase of pandemic demonstrated that most of the subjects belonged to the age group of 25-50 years. Many of these patients have associated with comorbidities, demanding the need of extra machineries and facilities.

Key challenges

The key challenges faced by the hospital faculties during the initial stages of COVID are as follows:

- Protection of healthcare workers and providing training on using protective measures and COVID-related protocols (many trainings have been conducted to improve the awareness of infection control measures)
- Motivation of healthcare workers.
- Increasing the number of intensive care beds to meet the requirement.
- Providing guidance on infrastructure and facilities of other institutions across the country.
- Creating awareness on COVID and guidance on interaction between staff and public.

Considering the pressing situation, effective response strategies have been developed by the AIIMS team to deal these challenges and the same has been briefed below:

Strategic responses

As an immediate response, on February 2020, The AIIMS has set up a COVID -19 task force constituting the following committees:

- Resource management committee
- Human resource committee
- Medical management-related committee
- Institutional Ethics Committee
- Committee for training consultants
- Diagnostic management committee

The primary objective of the task force is to ensure the proper functioning of all the departments.

The task force conducted daily meeting with faculty members and nursing officers, reorganization/ prioritization of hospital services, and overseeing of emergency services. The strategic response action plan included development of infrastructure, human resource planning, process re-designing (training, procurement and stock management), testing, communication and education, research on COVID-19, academics, and donation to 'PM CARES Fund.

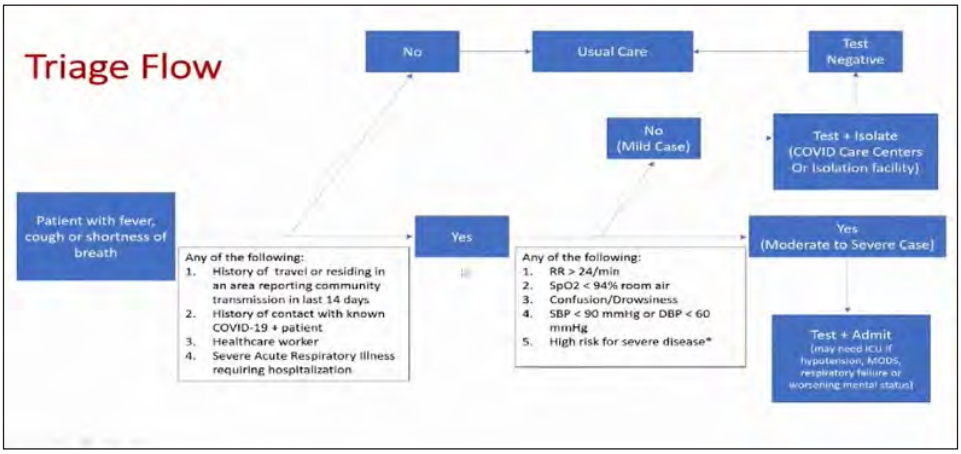
Infrastructure

The following infrastructure modifications/ reorganization were conducted as a part of COVID management response plan:

- Vishram Sadan converted to COVID care center with wards and ICU facility.
- Jai Prakash Narayan Apex Trauma Center (JPNATC) converted to COVID hospital by shifting trauma causes to main hospital.
- Main hospital equipped with fever clinic, emergency care and screening wards.
- Nearly1710 COVID beds and ICU beds were created.

During the peak, on an average 800-900 patients/day were treated at AIIMS and an effective triage flow plan was used for segregating patients (Fig. 5). Restoration of hospital services post lockdown was carried out effectively.

Fig. 5: Triage flow plan for segregating patients



The hospital has procured machinery and equipment (ventilators, high-flow nasal cannulas etc.), PPEs and other protective measures, buffer stock of key supplies, and dialysis machines exclusively for COVID patients.

Human resource planning

The planning of human resources included designation of nodal officers and teams for COVID- 19, and rostering and rotation of faculty, residents and staff. Transportation for AIIMS staff and temporary accommodation for the doctors/ staff posted in COVID-19 specified areas were arranged.

The test facilities of the hospital have been improved by adding real-time polymerase chain reaction (RT-PCR) test, CBNAAT (cartridge based nucleic acid amplification test) and rapid antigen testing.

Validation of test kits were also provided.

Teleconsultation

The hospital is currently running the "COVID-19 National Teleconsultation Centre" (CoNTeC) on behalf of the Ministry of Health and Family Welfare, Government of India. The center is catering to clinicians across the country, who want to consult our faculties for the management of COVID-19 patients, as well as to the public. Teleconsultation has been provided to nearly 155400 COVID and non-COVID patients.[9]

Training

Training of staff for COVID care-related practices was carried out through webinars, online training modules and videos. E-platform used for these webinars were SARAL and ONTOP. Nearly 13,262 AIIMS employees were trained on infection control practices after onset of COVID 19 pandemic, and 2212 AIIMS doctors, interns, nursing officers and OTAs registered for COVID 19 special training course through the SET facility on the SARAL platform. [10,11]

The national and international training courses carried out across the country are briefed below:[3]

National training

- Clinical excellence program in each state
- National e-ICU twice a week and covered 300 hospitals
- Capacity building for COVID-19 testing in 50 mentoring institutions across the country. More than 2000 labs were equipped for COVID 19 testing.
- National Clinical Grand round on every Wednesday

International training

1. Video conference series on COVID 19 for SAARC countries
2. Management of COVID 19
3. Infection control measures in hospitals
4. Bio- medical waste management
5. Laboratory diagnostics for SARS Co-2

AIIMS faculties have also attended video conference series on COVID-19 for SARRC countries.

Research

AIIMS has constituted a research committee exclusively for overseeing COVID-19 related research. Emergency meeting for ethics committee was conducted regularly and clearance was given for 63 research projects related to COVID-19. For facilitating the funds for COVID research extramural research grants (WHO, ICMR, CSIR) and intramural research grants (AIIMS) have been established. AIIMS is the first institute to announce funding for COVID related research projects (intramural) on fast track mode.

The institute was able to publish 190 papers in various national and international journals related to COVID 19. Out of these, 58% were inter-institutional collaborative research. Important research works done and published by AIIMS are listed below:

- Use of deep neural networks to analyze chest X-rays for diagnosis of COVID
- Machine learning-based triaging of patients based on the need for hospitalization
- Randomized controlled trial of ivermectin in COVID-19
- AIIMS-NCI preliminary data on co-infection of TB, HIV, hepatitis, dengue, aspergillus mucormycosis etc.
- Correlation between the COVID-19 and tuberculosis behaviors
- NCI-AIIMS patients with malignancies (n=4200). Prognosis and behaviour of malignant patients during COVID 19.
- Poor outcomes in patients with cirrhosis and COVID-19
- Outcome of conservative therapy in COVID-19 patients presenting with gastrointestinal bleeding

Information, Education and Communication

The AIIMS doctors are providing guidance on effective clinical management of COVID patients in the ICUs of different state hospitals through tele/video consultation. They are also continuously striving to improve the awareness of clinicians and public through various modes such as information booklets, COVID portal/videos, webinars, training – national and international, national helplines and guidelines.

Conclusion

Both the faculty members and management have been actively involved in combating the epidemic, using their respective strengths to play their roles. The united effort and response strategies may serve as a model to the global community in fighting the COVID-19 pandemic, in terms of coordination, decisiveness, solidarity and leadership.

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Controversies in COVID -19 management

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Introduction

COVID-19 infection, which first reported as a cluster of pneumonia from Wuhan, China, in December 2019, has rapidly emerged as a global pandemic.[1] During the early course of the pandemic, Italy had the highest infection burden and India remained much less affected with corresponding mortality rates of 14.24% and 3.03%.[2] However, the recent trends from the country shows an exponential increase in daily spike and the total cases has crossed 91 lakh mark, according to the Health Ministry data published on November 24, 2020.[3] The officially confirmed deaths from the disease is around 1,34,273. The present paper deals with controversies in the care of confirmed COVID cases.

Timeline and controversies related to drug use

Hydroxychloroquine/chloroquine

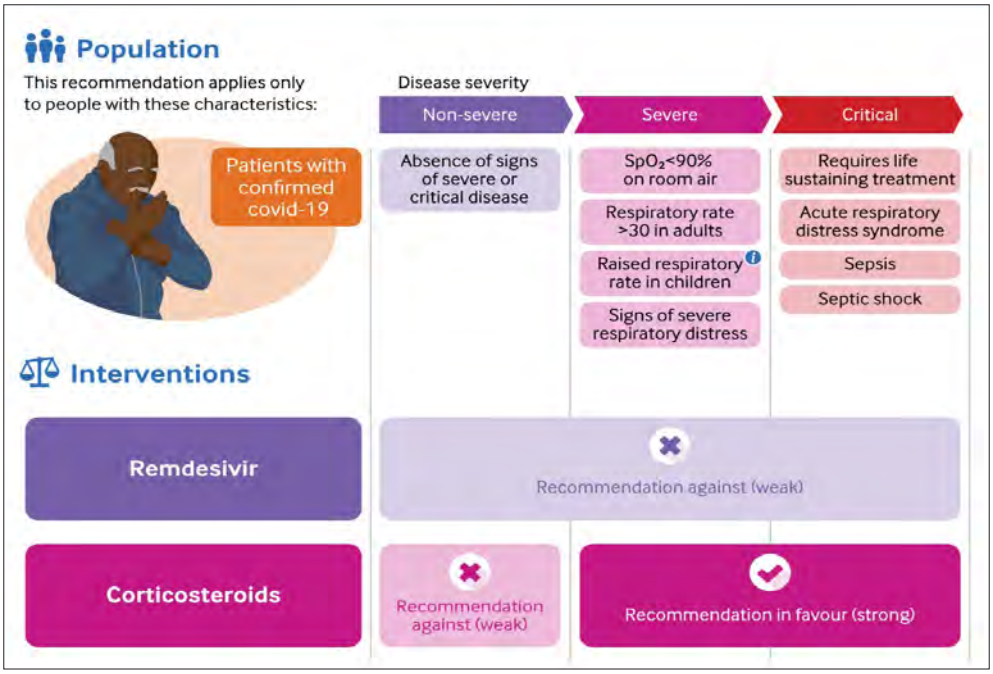
In March 2020, FDA has issued an emergency authorization for the use of hydroxychloroquine / chloroquine (HCQ/CQ) for managing hospitalized patients with COVID-19. However, in April 2020, FDA released a statement cautioning against the use of the drugs for COVID-19 outside the hospital setting or in a clinical trial due to increased risk of arrhythmias. In June 2020, citing the lack of efficacy and concern for safety signals noted in clinical trials, the FDA revoked the Emergency Use Authorization for HCQ/CQ.

The recent study published by the RECOVERY Collaborative Group has concluded that the HCQ treatment for hospitalized COVID-19 patients did not reduce the incidence of deaths at 28 days as opposed to those who had usual care.[4] Similarly, an international collaborative meta-analysis of randomized trials published by Axfors et al. has reported that the HCQ/CQ treatments are not beneficial in terms of the patient survival and HCQ was associated with increased mortality (OR 1.18). One concern pertaining to this meta-analysis is that, though nearly 100 authors contributed to the article, there was no clear representation from India.[5]

Remdesivir

Following the preprint publication of the WHO SOLIDARITY trial results in October 2020, the WHO has released the living guidelines on the drugs for COVID19. Figure 1 depicts the patient characteristics and summary of the WHO recommendations.

Fig. 1: Summary of WHO recommendations for COVID-19 drugs



The WHO recommendation is based on a systematic review and meta-analysis of four randomised trials involving 7,333 hospitalized subjects for COVID-19. The meta-analysis included the NIAID-ACTT-1 trial as well as the Solidarity trial. The comparison between ACTT-1 and Solidarity trials is given in figure 2. The former is a pharma-sponsored, double-blind placebo-controlled study to assess the time to recovery. Whereas, the Solidarity trial is an open labeled, WHO-sponsored study evaluating in-hospital mortality.

Figure 2: Comparison of ACTT-1 and Solidarity COVID-19 trials

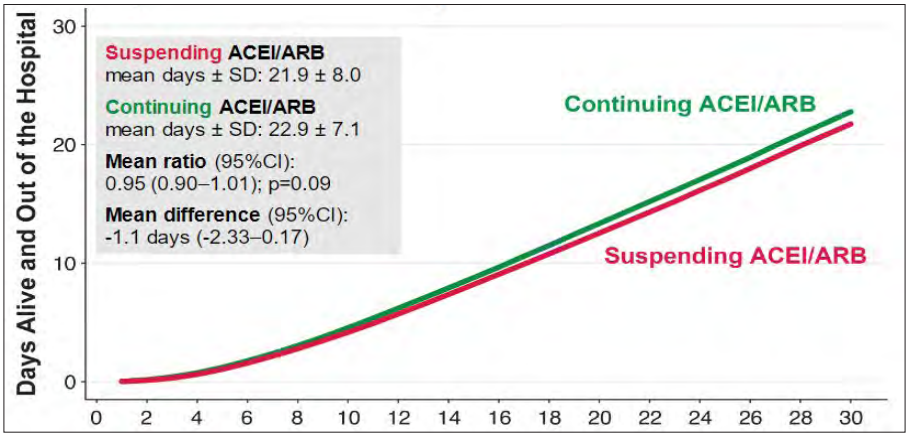
Trial Characteristic	ACTT-1	Solidarity, remdesivir arm
Intervention	**Remdesivir** vs. Placebo for up to 10 days	**Remdesivir** vs. standard care for up to 10 days
Sponsor	NIAID/DMID (USA)	WHO
Sites, Countries	73 sites, 10 countries	405 sites, 30 countries
Randomized	Yes (1:1)	Yes (1:1:n, shared controls if >2)
Blinding	Double blind	Open label
Placebo controlled	Yes	No
Stratification	By site, disease severity	Unclear: preprint yes, protocol, ?
Primary endpoint	Time to recovery (based on **WHO** ordinal scale)	In-hospital mortality
Sample size, primary analysis	The study was designed to achieve 85% power for detecting a recovery rate ratio of 1.35 with a two-sided type-I error rate of 5%. Enrollment to ensure at least 400 recoveries and to address subgroup analysis.	Bigger is better, can't estimate a sample size… Pairwise comparisons of intervention and its controls, intent-to-treat analyses of death rate ratios stratified by ventilated vs non ventilated patients x 3 age groups.

The ACTT-1 findings demonstrated that subjects belonging to the remdesivir group had a significantly shorter time to recovery than those in the placebo. In addition, the recovery was more pronounced in the patients who were hospitalized and required supplemental oxygen (rate ratio for recovery 1.47; 95% CI 1.17-1.84). The study also showed that the treatment benefits were more prominent in patients who received remdesivir ≤6 days, thereby suggesting the usefulness of early introduction.[6] Based on the clinical experience, upfront use (day 1 or 2) of remdesivir is advisable in high-risk groups (obese, elderly and subjects with comorbidities). Some of the limitations that deter its use in clinical practice are increased cost and need of IV administration.

ACE Inhibitors & ARBs

ACE2 has garnered greater interest as the cellular receptor of SARS-CoV-2. As opposed to the previous belief, it has been noted that the viral entry and replication cause down regulation of ACE2 receptors, thereby hindering the metabolization of ANG1 and II.[7] This may facilitate acute lung injury, adverse myocardial remodeling, vasoconstriction etc. Hence the use of ACE inhibitors and ARBs that inhibit the function of ANG1 and II may be beneficial in COVID patients, but there is a lack of literature evidence to corroborate the use and recommend them in clinical practice. Moreover, suspending the treatment in patients who are already on ACE inhibitors or ARBs is not necessary, unless there are any contraindications. The BRACE-Corona trial has concluded that suspending or continuing the ACE inhibiters/ ARBs did not improve the number of days alive and out of the hospital through 30 days (Fig. 3).[8]

Fig. 3: Comparison of primary outcome between continuing vs suspended ACEI/ARB groups



Thromboprophylaxis

The pathology of COVID-19 clearly indicates the association between thrombosis and inflammation and the disease generally appear as severe coagulopathy. Heparin therapy and thromboprophylaxis with heparin for managing medical inpatients remain controversial.[9] The areas of controversies are thromboprophylaxis for high risk patients undergoing home treatment, intensity of anticoagulation for inpatients, and the need for post discharge prophylaxis. Although several guidelines have been put forth by various societies, there is no clear consensus on the appropriate management strategies (Fig.4).

Fig.4: Guidelines on anticoagulation management from various societies

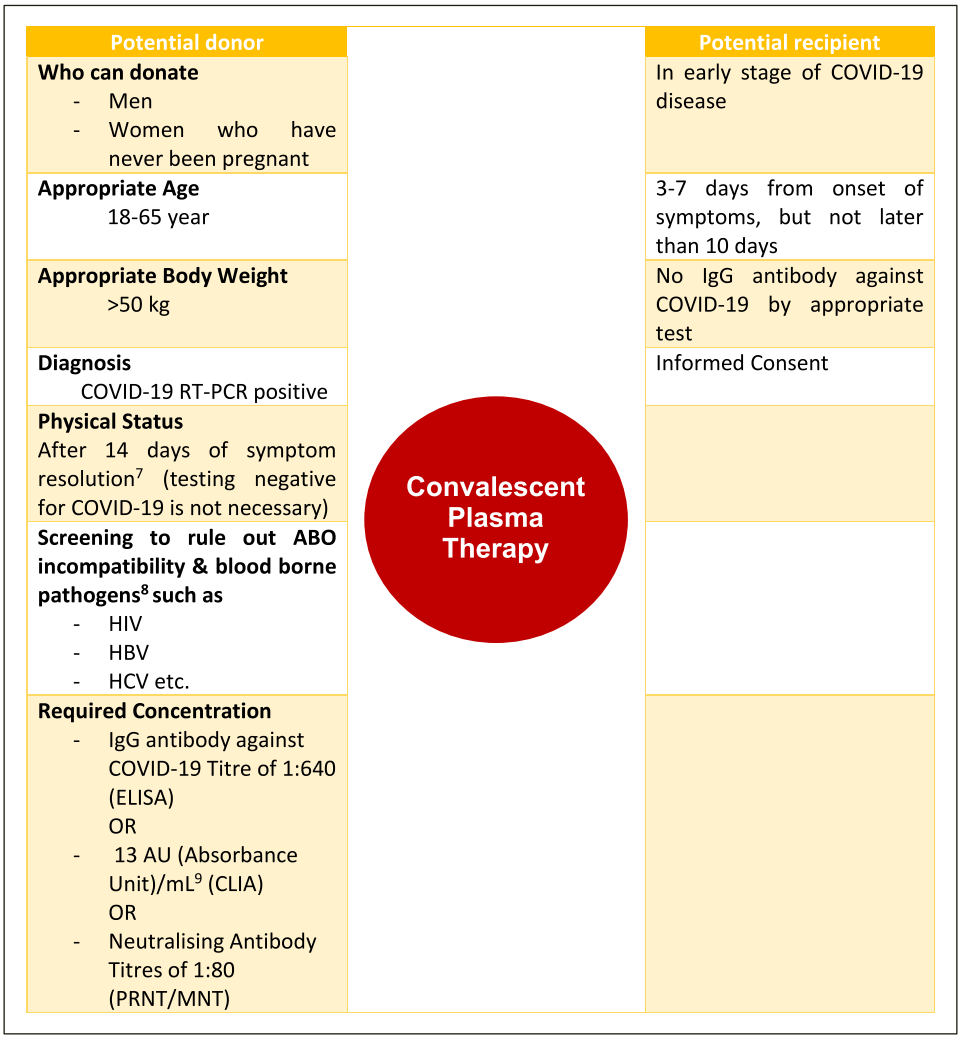
	ISTH[17]	ASH[18]	AC FORUM[19]	Mass General Hospital[67]	American Venous Forum[64]	Joint ISTH, NATF, ESVM, IUA[66]
DVT PROPHYLAXIS HOSPITAL	All Covid patients without contraindications	All patients LMWH or **Fondaparinux.** No recommendations on dose escalations recommend randomized trials	All Covid patients without contraindications	LMWH favored for all patients without contraindications Dose escalation not recommended	All Covid patients without bleeding contraindications Double dose **if** Caprini score over 8 or if BMI over 35	For hospitalized pts with **comorbidities** resp.failure, immobilized **if** no contraindications. Escalation not specifically addressed
DVT Prophylaxis post discharge	Not specifically addressed	Decide based upon status at discharge	Do risk assessment at discharge. Not all patients need post discharge prophylaxis	Not directly addressed	For Caprini score over 8 or BMI over 35 6 weeks of prophylactic dose AC	Risk stratfication
DVT or PE	Full dose anticoagulation 3 months. Switch **from** heparin preparation to oral med post discharge	Full dose LMWH or UFH 3 months Switch to po med post d/c	LMWH over UFH 3 months Switch to po med post d/c	LMWH over UFH 3 months Switch to po med post d/c	3 Months UFH or LMWH Switch to oral anticoagulant post d/c	3 months full dose anticoagulation
Cytokine and thrombotic storm no measurable DVT or PE	Full dose heparin not addressed Consider experimental therapies	Full dose heparin not addressed	Not specifically addressed	Don't recommend Full dose AC in absence of DVT or PE. If high clinical likelihood of DVT and/or PE and testing impossible only then consider therapeutic AC	For D Dimer over 3 full doses recheck Ultrasound at 2 weeks. If no DVT at 6 wks give prophylaxis dose for 3 months, if DVT or PE 3 Months therapeutic dose	Unknown what constitutes best dosage
Other Details	If D Dimer markedly raised admit even if no other indications	DOACs better than VKAs post discharge particularly if isolation desired	Use **anti** Xa levels for monitoring Do not recommend TPA	Do not recommend TPA	Venous duplex only if it will change management	LMWH heparin preferred for AC but heparin for impending procedures. Numerous Covid drugs have interactions with anti platelet meds

As per the author's clinical experience, the potential risk for venous thromboembolism (VTE) in high risk patients undergoing home treatment can be assessed using Padua prediction score or IMPROVE VTE risk score. Patients having high D-dimer and on home prophylaxis, prescribing aspirin may be ideal, and those at high risk or had a history of deep venous thrombosis (DVT), non-vitamin K oral anticoagulants (NOACs) are advisable. Elevated D-dimer levels in discharged patients can also occur due to inflammation. Hence full-fledged pharmacological thromboprophylaxis may not be needed in admitted patients, unless there is established DVT/PE. For patients in ICU, a slightly intensified prophylaxis is recommended. In patients with persistent D-dimer levels, aspirin may be added as prophylactic treatment. A certain extent of post-discharge prophylaxis (probably for 4 weeks) is advisable in patients with risk factors and in those having history of PE/DVT. These observations are purely based on the author's clinical experience.

Convalescent plasma

The PLACID trial by Agarwal et al. has evaluated the effectiveness of convalescent plasma to treat moderate COVID-19 in adults in India. The study results showed that in settings with limited lab capacity, the treatment did not reduce 28 day mortality or progression to severe stages. However, the treatment was linked to earlier resolution of fatigue, shortness of breath and higher negative conversion of SARS-CoV-2 RNA. The researchers have concluded on the limited effectiveness of convalescent plasma in patients with moderate COVID.[10] It is necessary to measure the neutralizing antibody titers both in the donors and the recipient prior to the initiation of plasma therapy. In addition, the risk of thrombosis also needs to be evaluated in candidate plasma recipient. The ICMR guidelines for convalescent plasma therapy are depicted in figure 5. [11]

Fig. 5: The ICMR guidelines for convalescent plasma therapy



Tociluzimab

The indiscriminate use of tociluzimab may cause more harm than good, as the treatment may increase the risk of exotic infections. Similarly, majority of the tocilizumab studies have not shown any benefits in mortality reduction in COVID patients. Comparison of major tociluzimab studies have shown that most of the studies have been carried out in severe or moderately ill patients, and very few studies have evaluated critically ill patients requiring ventilation support.[12] In contrast to these findings, recently published results of the Remap-Cap international platform trial have reported that the treatment outcomes are better in critically ill COVID patients receiving tocilizumab as opposed to subjects who received no immune modulator (OR 1.87).[13] In view of mixed study findings, large evidence-based trials are warranted to corroborate the effectiveness of the drug in managing COVID.

Conclusion

After initial assessment and surveillance, a concerted effort for providing timely care based on the international guidelines can help Physicians avert adverse outcomes and improve clinical outcomes.

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COVID-19 diagnosis: what do we know so far, including diagnostic pitfalls

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogenic organism causing COVID-19, is a respiratory virus primarily spreading through droplets of saliva or nasal discharge of an infected person. It may also spread by touching surfaces contaminated with the viruses.[1] Following the declaration of COVID-19 as a pandemic, diagnostic field has witnessed the development of newer diagnostic strategies with improved efficacy and sensitivity. The present discussion primarily focuses on current testing methods and their diagnostic pitfalls.

When do you suspect COVID-19?

The classic symptoms to suspect COVID-19 infection include fever, respiratory symptoms (coryza, sore throat, cough, dyspnea), muscle pain, chills, conjunctivitis, loss of taste or smell, headache, nausea, diarrhea and hepatitis. Though the disease is marked by severe clinical manifestations of lower respiratory tract, it may involve other organs due to viral dissemination.[2] The disease should be suspected in individuals presenting with any of these symptoms, especially in residents or those who have travelled to an area with community transmission of COVID-19. The chances of household contact are estimated to be around 10% - 40%.[3] The risk of contracting COVID-19 is high in subjects with complications related to thrombosis, which can typically present as myocardial infarction, abdominal vascular ischemia, cerebrovascular accident or some uncommon events like multisystem inflammatory syndrome.[4]

Diagnosis of COVID-19

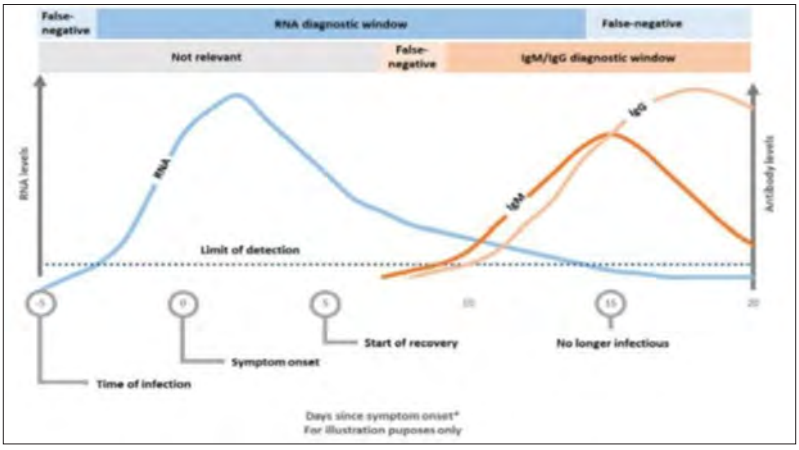
Primarily two types of tests are available for COVID-19, viral tests and antibody tests. The viral tests, which reflects current infection, are designed to detect the virus. In contrast, the antibody tests are indirect tests, which ascertain seroconversion to previous infection, or early seroconversion to ongoing infection.[5] The various currently available diagnostic methods are listed below:

1. Direct tests to identify the genetic elements of the virus include:
   - **Antigen tests**: Less expensive and need nasopharyngeal or oropharyngeal swab
   - **RT-PCR** (reverse-transcription polymerase chain reaction): Considered as gold standard for diagnosing COVID
   - **TrueNat**: A cost-effective method to detect COVID virus in the sputum sample in less than an hour[6]
   - **Gene Xpert / CBNAT**: A cartridge-based TB detection test
   - **Isothermal amplification, CRISPR, NGS** are next generation tests
2. Indirect or antibody tests
3. Supplementary or imaging tests

Timelines of diagnostic tests

RNA levels can be detected 3 days before the symptoms onset and may persist for 7-8 days on an average. RT-PCR can detect viral RNA up to 2-3 weeks after the symptom onset. The specificity for IgM and IgG for diagnosing COVID is > 95% and the antibodies may appear in blood 4-5 days after the disease onset and may increase the levels by 2-3 weeks. In most of the subjects, seroconversion occurs by 3rd or 4th week (Fig.1). The IgM levels gradually reduces by 7th week and the IgG antibody levels persist for one year or more. [7]

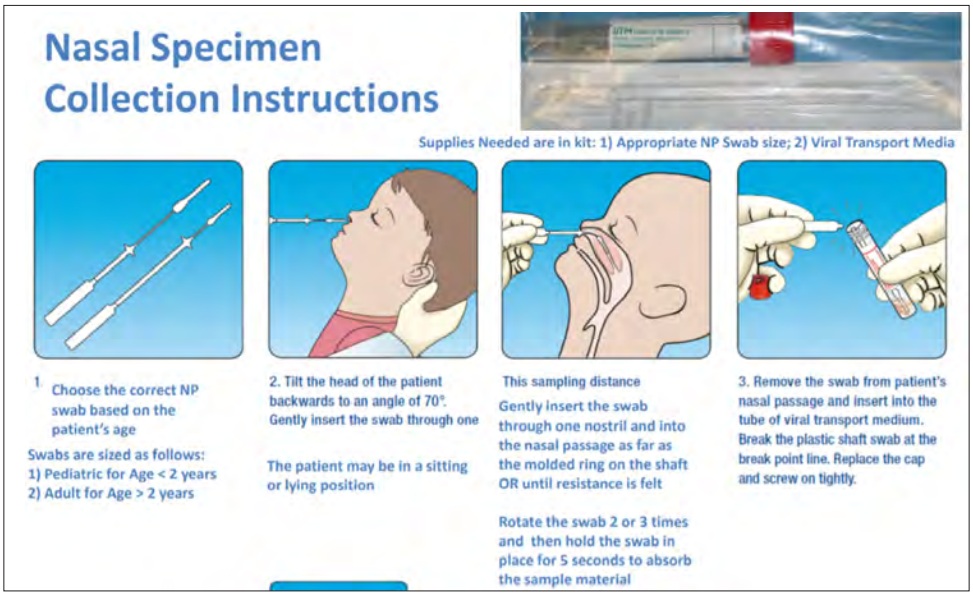
Fig.1: Timelines of COVID diagnostic tests



Antigen test

The rapid antigen test (RADT) for COVID-19 is a rapid, point-of-care nasopharyngeal swab test that directly detects the presence or absence of coronavirus antigen. The test is designed to detect a specific protein in the virus, which elicits the body's immune response, and generates the diagnosis result typically within 30 minutes. The test's specificity is about 95%, but the sensitivity is as low as 50%-60%. It is a bedside test and comparatively less expensive than RT-PCR.[8] For the proper implementation of the government's strategy to test, track and treat, the ICMR has recommended antigen test for initial screening of COVID-19 in high risk population and further confirmation of the findings through RT-PCR test.[9] Instructions for collecting nasal specimen are depicted in figure 1.

Fig. 2: Instructions for collecting nasal specimen



RT-PCR test

The test is considered as gold standard for diagnosing COVID and it is based on probes to detect gene elements. These gene targets can be either envelope gene, spike protein, nucleocapsid or the RNA dependent-RNA polymerase gene. Cycle threshold (Ct), the semiquantitative measure of SARS-CoV-2 viral load, refers to the number of cycles required to amplify the genetic element. Ct values are inversely related to viral load and serves as an indirect method of quantifying the copy number of viral RNA in the specimen. Although cycle thresholds <25 cycles indicate the infection, it is not a clinically standardized indicator.[10] RT-PCR can be positive 2-3 days prior to symptom onset and may remain positive for 2-3 weeks or longer. Hence, a positive RT-PCR does not conclude on the presence of a genetic viable virus element, and it only indicates that the patient has had COVID past 2-3 weeks ago. A positive RT-PCR test assists in diagnosing COVID, but does not confirm the infectivity, and a negative test does not rule out the possibility of COVID. The sensitivities of PCR done using different samples types are given in figure 3. The highest sensitivity for RT-PCR has been noted for bronchoalveolar lavage (93-95%), followed by sputum specimen (72-75%).[11]

Fig. 3: Sensitivity of PCR done using different samples types

Sample type	Sensitivity
Nasal swab [5]	63%
Pharyngeal swab [5]	32%
Feces [5, 18]	48.1%
Blood [5, 18]	1–3%
Sputum [5, 18]	72–75%
Bronchoalveolar lavage [5, 18]	93–95%

The occurrence of false negative results in RT-PCR could be due to inappropriate timing of the specimen, type of specimen used, improper technique of testing and intrinsic test variability. False positive result can occur due to reagent contamination or other technical issues.[12] Equivocal results are reported, if only one antigenic determinant gene turns positive, and it is paramount to repeat the test in 24-48 hrs. It is not recommended to repeat the test to confirm the clearance of the virus (may show positive for several weeks).

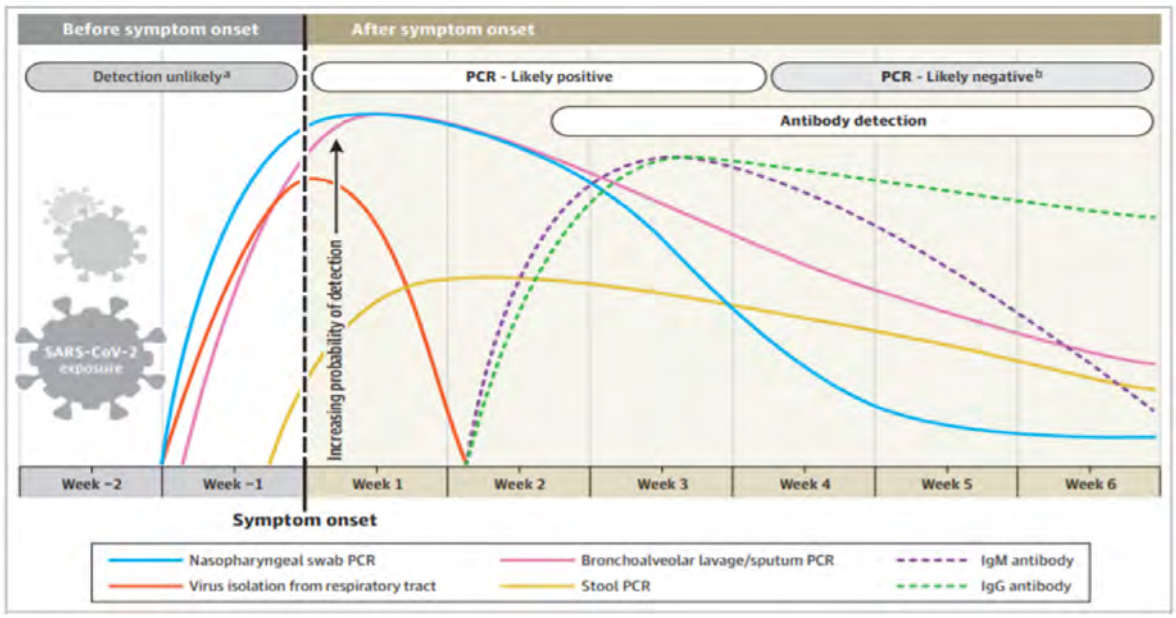
Antibody tests

The 3 main uses of antibody tests are as follows:

- To detect mild to moderate infections during the later stages of illness
- Diagnosing the seroprevalence in the community with regard to SARS COV-2

- Suspecting multisystem inflammation after recovering from COVID
- IgM and IgG may appear in blood 4-5 days after the disease onset and the seroconversion may occur within 3-4 weeks. IgM peaks about 7 weeks after the disease onset and recedes gradually, but IgG levels may persist for several months. The specificity of the antibody testing is around 97% and the sensitivity may depend on the time of testing.[13] Figure 4 depicts various diagnostic tests available for diagnosing SARS COV-2.

Fig.4: Various diagnostic tests for SARS COV-2



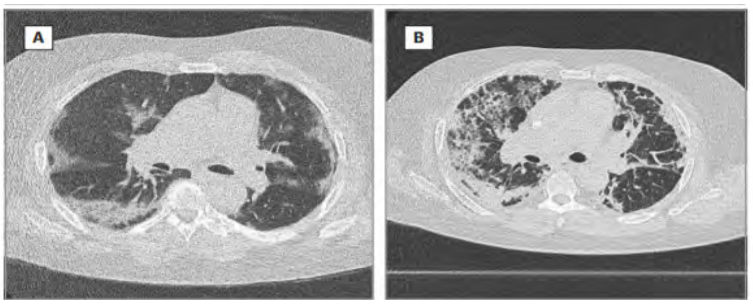
Imaging studies

It is based on the likelihood of the person having features of the disease based on the COVID-19 Reporting and Data System (CO-RADS) score.[14] The score 5 indicates high possibility of COVID and in such patients CT Severity Index (CSI) is carried out to evaluate the viral distribution in the lung. The characteristic abnormalities of the lungs noted in CSI are as follows:[15]

- Peripheral ground-glass opacities (GGOs)
- Ill-defined margins
- Air-bronchograms
- Inter-lobular septal thickening
- Thickening of adjacent pleura

Imaging studies are non-specific, and CT is recommended only if the RT-PCR test is not available, delayed or negative, and COVID is strongly suspected. CT scan showing GGO opacities is given in figure 5.[16]

Fig.5: CT scan showing GGO opacities



Biomarkers

C-reactive protein, procalcitonin, D-dimer, LDH, ferritin, troponin I, and IL-6 are the commonly used biomarkers and they are ideal for risk stratification in critically ill patients with hyperinflammation.[17] These tests are nonspecific, and are relevant only if a COVID patient requires hospitalization and to predict the prognosis.

Conclusion

Direct tests (antigen tests and RT-PCR) are specific for diagnosis of acute COVID-19. The clinical significance of cycle threshold values has not yet validated. Repeat PCR nasopharyngeal and oropharyngeal tests are not advisable due to the presence of viral genetic elements for several weeks. Antibody tests are useful for late diagnosis or serosurveillance. Imaging studies are non-specific and CT scan for asymptomatic COVID-19 suspects is not recommended.

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COVID-19 and Comorbidities

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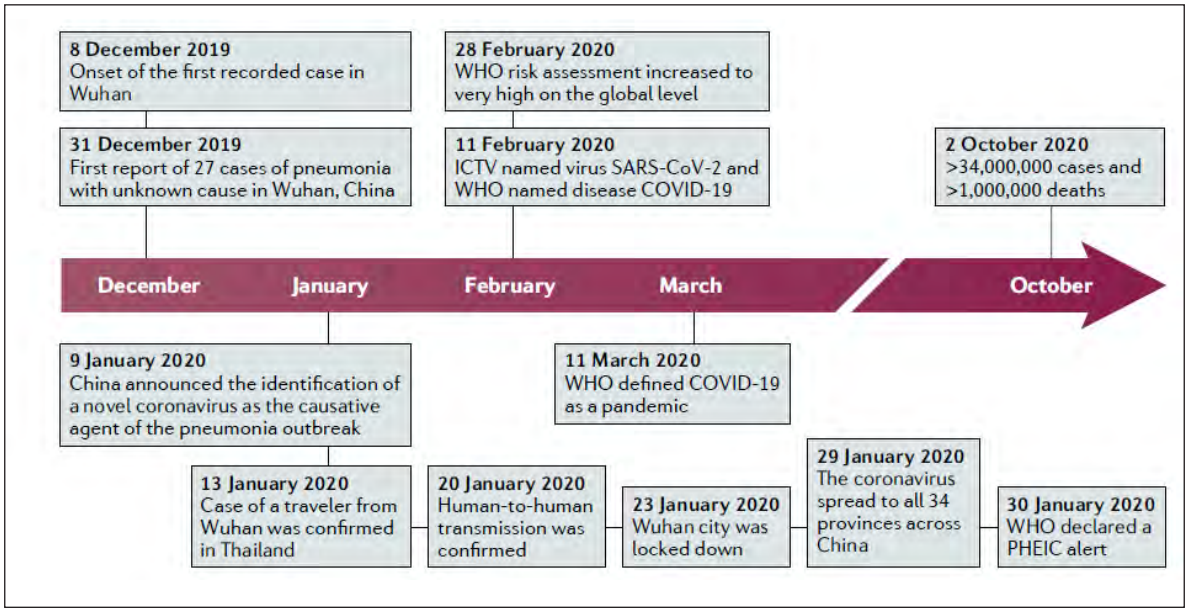
Introduction

The first recorded case of COVID19 was reported on 8th December 2019, followed by a cluster of cases of pneumonia in Wuhan, Hubei Province of China. In February 2020, WHO has increased risk assessment to the global level and the disease has been named as 'COVID-19' (Fig.1). WHO has declared it as a global pandemic, as the disease has spread to nearly all the continents and the cases are rising at an exponential rate. In India, the case load has surpassed 91 lakh and many states are witnessing a resurgence of infection. The new resurgence status indicates the persistence of infection in the year 2021.[1]

Fig.1: Timeline of COVID



COVID: Global scenario

As per the WHO COVID-19 status update for November 7, 2020, the number of confirmed cases and deaths were 48,786,440 and 1,234,834 respectively.[2] Despite the silent threat, many countries have begun to introduce relaxation of lockdown and reopening of public spaces, and religious, businesses and other institutions with stringent safety protocols. Although the second and even a third wave of infection are imminent, economic activities and normal human activities cannot be restricted further for an indefinite period.

COVID and Comorbidities

The term 'comorbidity' is defined as the simultaneous presence of two or more diseases or medical conditions in a patient. The co-existence of two or more comorbidities, termed as 'multimorbidity, is often noted e.g. diabetes and hypertension, hypertension and CVD. According to the global estimate by a modelling study, nearly 1.7 billion individuals have at least one underlying health condition and it comprises of 22% of the global population.[3] The presence of pre-existing co-morbidities such as CVD, hypertension, diabetes, congestive heart failure, chronic kidney disease, and cancer in hospitalized COVID-19 patients with increases the risk of morbidity and mortality due to infection.[4]

The risk of contracting COVID in patients with underlying comorbidities is similar to that of general population. However, increased COVID severity and need for hospitalization, ICU care, and mechanical ventilation have been noted in patients with comorbidities.[5]

Determinants of comorbidity

A study by Deng et al. re-analyzed the largest confirmed case series published by China center involving 44,672 patients. The study has noted that male subjects had nearly 1.7-fold higher risk of death as opposed to female patients. Moreover, the researchers noted that patients with comorbidities had a significantly high death risk. Among the 44672 confirmed COVID cases, 1023 (2%) mortality deaths were identified, and hypertension, diabetes, CVD, respiratory disease and cancer were identified as the main risk factors contributing to increased mortality.[6]

Age and gender are the 2 well-established risk factors for severe COVID-19 outcomes. The study involving around 44,000 patients from China has reported 15% mortality in patients >80 years of age and only 0.2% in subjects <40 years of age. In UK, 90% of the deaths due to COVID has been reported in subjects >60 years of age. In India, the mortality rates reported in subjects >50 and <50 of age were 65% and 35% respectively.[7] In addition, male gender is linked to 60% increased risk for COVID mortality as opposed to females.[8] With regard to ethnicity, 45% increased risk of death has been noted among South Asians.[9]

According to CDC, comorbidities such as hypertension, diabetes mellitus, CVD, chronic kidney disease cancer, immunosuppression, HIV/AIDS, COPD/asthma, obesity, and pregnancy have been linked to adverse outcomes in COVID patients.[4] Evaluation of the COVID data from Victoria Medical College demonstrated that hypertension (34%) was the most common comorbid condition noted in hospitalized COVID patients, followed by diabetes (32%), CKD (9%), IHD (6%) etc. The incidence of various comorbidities noted in inpatients of Victoria hospital is listed in figure 2.

Fig. 2: The incidence of various comorbidities noted in inpatients of Victoria hospital

Diagnosis	No.	Percentage (%)
HTN	1659	33.95
DM	1560	31.92
CKD	458	9.37
IHD	307	6.28
Hypothyroidism	296	6.05
Malignancy	221	4.52
BA	147	3.00
COPD	58	1.18
CVA	56	1.14
TB	50	1.02
OSA	30	0.61
HIV	28	0.57
HBV	12	0.24
HCV	04	0.08

The correlation of COVID case mortalities (n=11430) occurred in the Karnataka state with comorbidities has shown that hypertension was the comorbidity noted in nearly 49% of the death cases, followed by diabetes (36%), COPD (10%), CAD (10%), CKD (8%) and cancer (2.5%). The data analysis demonstrated that the mortality rate was 4-5 times higher in patients with co-morbidities when compared to non-comorbid patients.

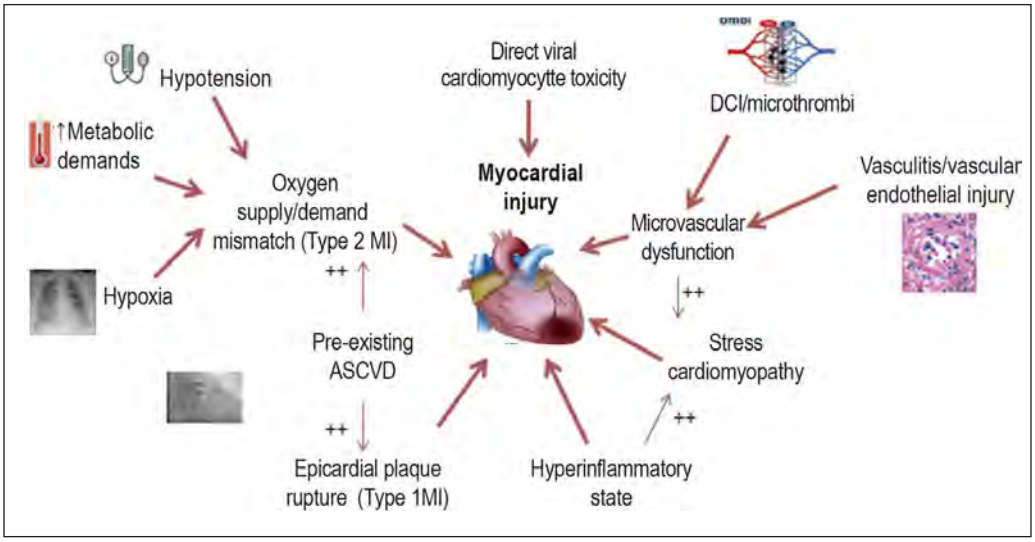
Epidemiology and pathophysiology of CVD in COVID-19

Study of 44,672 patients with COVID-19 found that a history of CVD was associated with a nearly five-fold increase in the case fatality rate when compared to patients without CVD (10.5% v/s 2.3%).[10] Literature studies have shown ACE2 as the cellular receptor of SARS-CoV-2 facilitating the viral entry into the host cell. The viral entry causes reduced expression of ACE-2, causing increased levels of angiotensin II leading to proinflammatory state and eventually dysregulated immune activation. ACE2 is expressed in various organs including heart, lungs, vascular cells and gastrointestinal system and this explains the multi-organ involvement noted in COVID-19 cases.[11]

Multiple mechanisms linked to cardiac injury and various manifestations noted in COVID patients have been briefed below (Fig. 3): [12]

- Direct injury to myocardium due to viral myocarditis
- Hyperinflammatory response causing destabilization and plaque rupture (type 1 myocardial infarction)
- Endothelial dysfunction caused by hypoxia and increased cytokine levels, resulting in thrombus formation
- Oxygen supply /demand mismatch (type 2 myocardial infarction)
- Direct viral cardiomyocyte toxicity
- Hyperinflammatory response and Microvascular dysfunction

Fig.3: Mechanisms linked to cardiac injury and various manifestations in COVID



Acute myocardial injury

Both ischemic and non-ischemic myocardial injuries have been noted in COVID patients with cardiac manifestations. Recent reports indicate that 22-30% of patients with severe covid-19 infections have acute myocardial injury. An MRI-based study involving COVID patients has noted that nearly 70% had microinjury to the heart, but most of these subjects demonstrated normal LV function in ECG.[13] The characteristics of ischemic and non-ischemic myocardial injuries are briefed below:[14]

Ischemic:

- Type I MI (due to plaque rupture)
- Type II MI (due to supply demand ischemia)
- Myocardial injury due to disseminated intravascular coagulation (DIC)

Non-ischemic:

- Myocarditis
- Stress induced cardiomyopathy
- Cytokine release syndrome

Comorbidities and adverse outcomes

Review of literature studies have shown that nearly 58% of the hospitalized COVID patients were comorbid as opposed to 42% with non-comorbid status. Uncontrolled blood pressure was reported in 23-33% patients with COVID and hypertension, and the mortality rate noted was 6%, as opposed to 1% in non-hypertensive patients.[15] No adverse effects have been reported upon continuing ACE-I or ARB therapy in COVID patients.[16] However, it is not advisable to initiate the treatment in patients diagnosed with COVID.

The clinical features noted in COVID patients with diabetes comorbidity include impaired phagocytosis and T cell function, weakened immune system, and increased ACE2 and blood sugar levels. The development of diabetes in non-diabetic and prediabetic patients has been noted following COVID infection.[17] Increased severity of COVID, including 8-9% mortality rate, has been reported in diabetics. Moreover, the prevalence of diabetes in fatal cases was found to be 32%.[18]

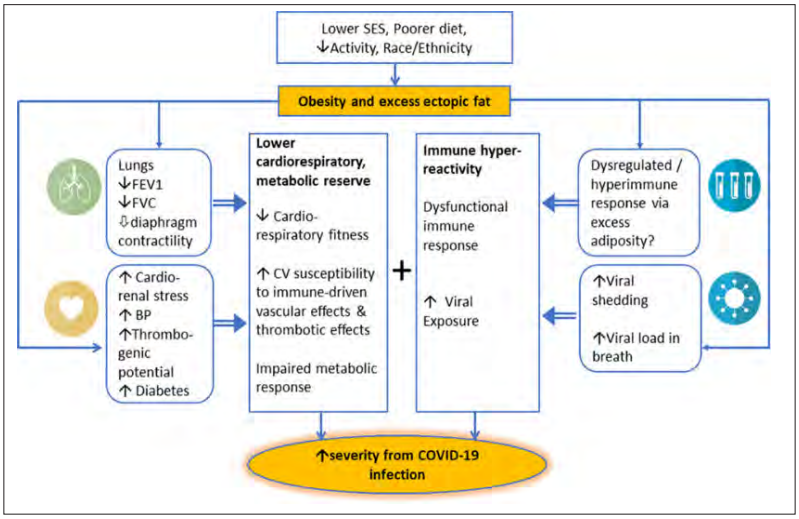
A small proportion of patients with cardiac comorbidities are at increased risk for developing bradyarrhythmia. Hence persistent monitoring of cardiac function is necessary for such patients. Even remote monitoring with wearable devices is recommended for those on home isolation.[19]

In Jayadeva Institute of Cardiovascular Sciences, around 411 patients with comorbidities and cardiovascular manifestations were managed for COVID-19. The median age of the treated patients was 57 years and nearly 188 were >60 years of age. The corresponding proportion of subjects noted with diabetes, hypertension, dyslipidmia, renal dysfunction, and cerebrovascular events were 41.8%, 38.4%, 6.3%, 12.4% and 1.7%. The corresponding proportion of subjects noted with diverse cardiovascular manifestations were as follows: acute MI: 829(20%), NSTEMI: 103 (25%), non-

ischemic acute myocardial injury: 77 (18.7%), heart failure: 171 (41.6%), cardiogenic shock: 10 (2.4%), arrhythmias: 34 (8.3%), QTc prolongation: 50 (12.1), DVT: 6 (1.5%) and PE: 3 (0.7%). A subgroup analysis was carried out to compare cardiovascular manifestations of COVID-19 and comorbidities between diabetics and non-diabetics. The analysis demonstrated that hypertension was more in diabetics as opposed to non-diabetics (65% vs. 20% P <0.001). In addition, mortality was found to be higher in former group than latter (20% vs. 12%, P <0.034). Hospital admission due to acute MI during pre-lockdown was found to be more (n=591) as opposed to lockdown period (n=311). However, around 5% increase in mortality was noted during lockdown when compared to pre-lockdown, and this could be attributed to changes in treatment strategies and management protocols.

Obesity has been identified as a major risk factor for adverse outcomes in COVID patients. The thin-fat phenotype noted among Asian Indians has been found to have an elevated risk for contracting COVID infections as well as other noncommunicable chronic diseases.[20] Moderate to severe obesity increases the severity of COVID-19 infection and the need for mechanical ventilation is more for obese individuals. The mortality rate noted in patients with BMI >35 was around 8-10% in contrast to 3.3% noted in non-obese patients.[21] The implications of COVID-19 in subjects with obesity and ectopic fat have been depicted in figure 4.

Fig. 4: Implications of COVID-19 in subjects with obesity and ectopic fat



Considering the elevated risk, the UK government has recommended SHIELDING, i.e. staying at home at all times and avoiding any face-to-face contact, for extremely vulnerable GROUPS for 3 months.[22]

Conclusion

It is imperative that patients with comorbidities need to take more precautions and limit social interactions to reduce the risk of contracting COVID-19. The management strategies include appropriate triaging, early introduction of treatment and constant monitoring and surveillance.

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Cytokine storm and Immunosuppression

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Introduction

First clusters of cases with pneumonia were reported in Wuhan, Hubei Province of China on 31st December 2019. As a result, by 1st January 2020, the seafood market was closed by Wuhan health authorities. By 7th January 2020, novel corona virus spread all over China and first case of COVID-19 outside China was reported on 13th January. Public health emergency of international concern was introduced in India upon reporting the first case on 30 January 2020, and on 11th March 2020, the disease was declared as a pandemic by WHO. It has been noted that nearly 20% of patients with moderate to severe infection demonstrated several severe outcomes such as acute respiratory distress syndrome (ARDS), multiorgan failure or even death.[1]

Basic virology

Other recently reported pandemic outbreaks were Severe Acute Respiratory Syndrome Corona Virus (SARS CoV) and Middle East respiratory syndrome (MERS CoV) occurred in 2003 and 2012 respectively. Considering the resemblance of 79% genome to SARS CoV, the present COVID-19 organism has been named as SARS CoV-2.

SARS-CoV-2 virus enters the host cell respiratory epithelium through interaction with ACE2 receptor, resulting in membrane fusion and viral genome release into the host cytoplasm. Transcription and replication lead to maturation and release of virus, resulting in infection, severe illness, and multisystem organ failure. The immune response of the host contributes to the release of excessive pro-inflammatory mediators in response to virus and may result in cytokine storm. [2]

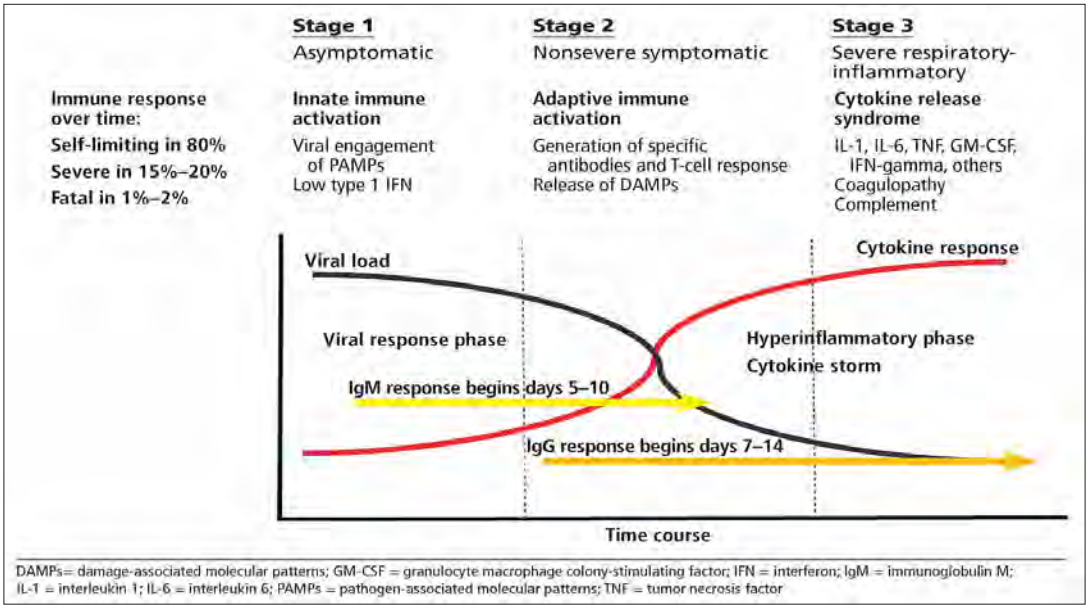
Stages of COVID illness

Stage 1, Asymptomatic: This stage is mainly asymptomatic and high level of viral shedding occurs in upper respiratory tract. Moreover, innate immune system act as initial mode of host defence (Fig 1).

Stage 2, Non-severe symptomatic: Stage 2 consists of non-severe symptoms, and viral replication loads peaks after 5 days of symptom onset. During this period, adaptive immunity triggers specific T and B cells response to end infectious process. This stage acts as a precursor to the next stage of severe illness. Some cases may tend to have serious symptoms and severe illness (Fig 1).

Stage 3, Severe respiratory inflammation: Stage 3 presents with severe respiratory illness marked by progressive fever, multiorgan dysfunction, hypercoagulability, and shock. It may progress to pneumonitis, causing respiratory failure due to alveolar damage. Adaptive immune response of host defence releases T cell and cytokines, ultimately causing cytokine storm manifested by IL-1, IL-6, TNF, GM-CSF, IFN-gamma, and other coagulopathy complements (Fig 1). [3]

Fig. 1: Three stages of COVID-19 illness

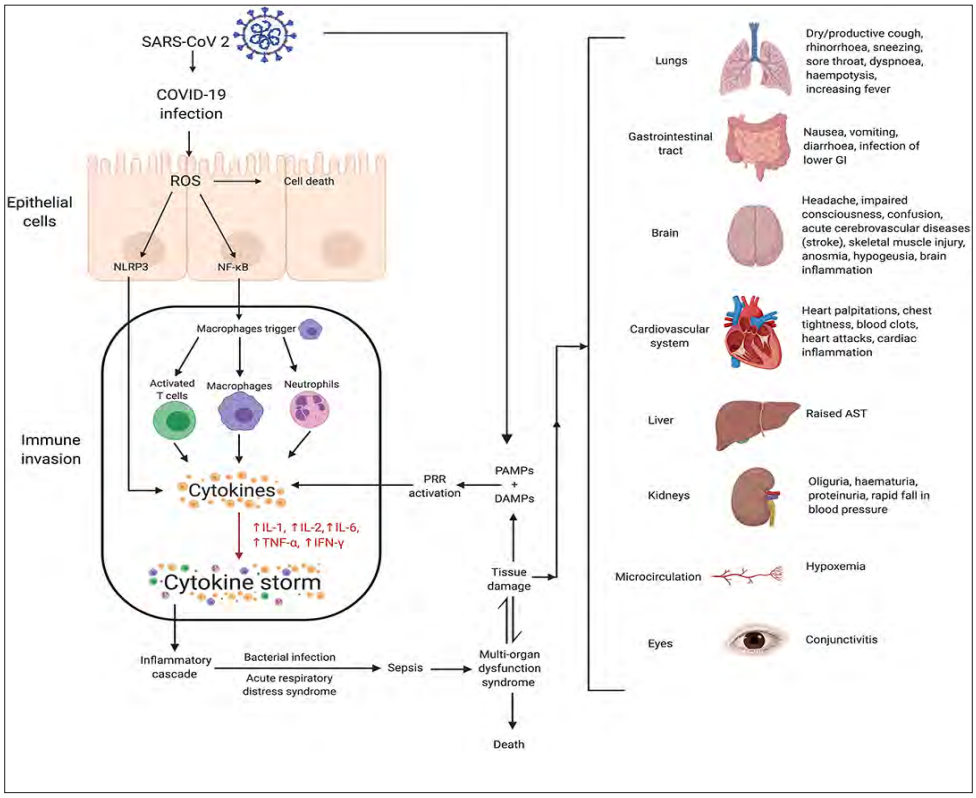


DAMPs= damage-associated molecular patterns; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IgM = immunoglobulin M; IL-1 = interleukin 1; IL-6 = interleukin 6; PAMPs = pathogen-associated molecular patterns; TNF = tumor necrosis factor

Stage 3 Illness and Cytokine storm

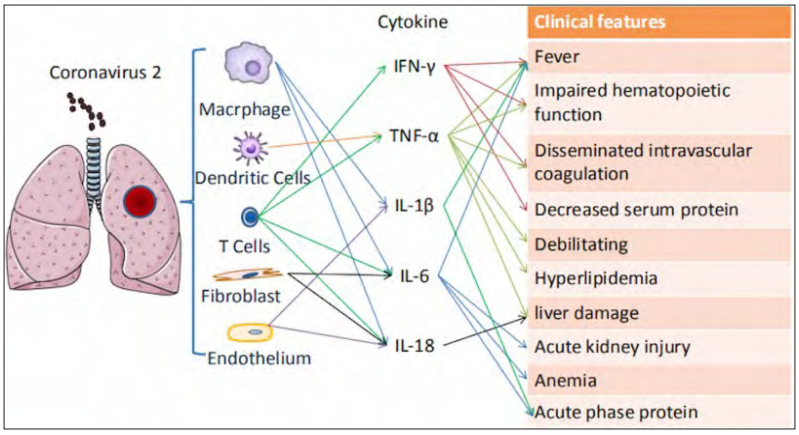
Primary viral infection may depend on pathogenicity and inflammation trigger by virus particle. Low interferon level and persistent strong inflammatory response contribute to continued active viral replication and strong inflammatory reaction. Suppression of T cells with marked increase in cytokines leads to cytokine storm, predominantly affecting the lungs. In children, it may present in a variant form known as multisystem inflammatory syndrome in children (MIS-C). Hyperinflammatory immune response stimulation caused by the virus facilitates the epithelial-cell mediated production of reactive oxygen species (ROS) and apoptosis. Synthesis of NLR3 and NF-kB, stimulated by ROS, also contributes to cytokine storm. The impact of cytokine storm on various organs is depicted in figure 2.[4]

Fig. 2: The impact of cytokine storm on various organs



Each cytokine manifests various pathogenic inflammatory responses and clinical features, thereby constituting a complex network of cytokine storm. Therefore, controlling inflammation by targeting one or two cytokines may not be helpful in manging COVID-19 infection or any other inflammation disease (Fig 3).5 A cytokine profile resembling secondary hemophagocytic lymphohistiocytosis (sHLH) is associated with COVID-19 disease severity.

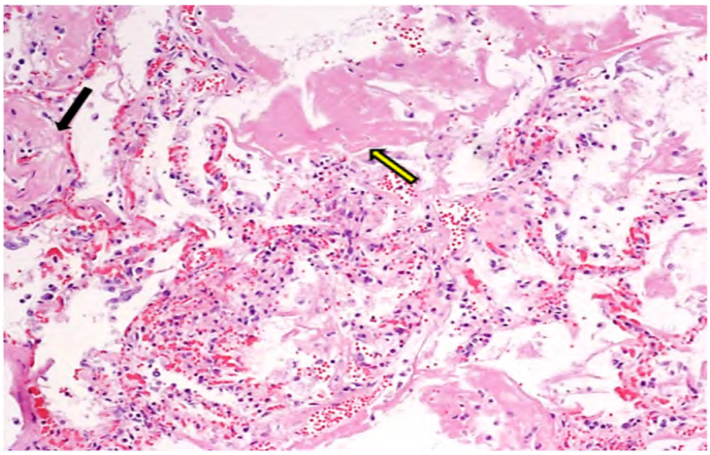
Fig. 3: Clinical features and pathogenic inflammatory response manifested by various cytokines



Histopathological findings

The histopathology evaluation of lung tissue of COVID-19 patients has demonstrated edema and inflammatory cell infiltration, resulting in exfoliation of alveolar epithelium. Scattered large protein globules (Fig. 4, yellow arrow), diffused alveolar damage (DAD) with fibrotic organisation and hyaline membrane (Fig 4, black arrow) have also been noted. Septal thickening of alveolar with inflammatory infiltrate and loss of integrity lead to alveolar infiltration, which ultimately progress to severe ARDS.[6]

Fig 4: histopathology of lung of patient with Covid-19



H score assists in investigating the likelihood of severity of viral illness. It is validated for the diagnosis of secondary sHLH and is suggested to detect hyperinflammatory states in COVID patients (Table 1).

Table 1: Parameters of H score

Known immunosuppression	Yes/no
Maximum temp	< 38.4, 38,4-39.4, >39.4
Hepatomegaly	Yes/No/Unknown
Splenomegaly	Yes/No/Unknown
Lower Hb	<9.2 or > 9.2 or unknown
Lower Leukocyte count	< 5000 or > 5000 or unknown
Higher ferritin level	< 2000, 2000 – 6000 or > 6000
Higher triglyceride level	< 1.5, 1.5 – 4.0, > 4.0
Higher AST/ALT level	< 30 or > 30
Lower Fibrinogen	< < 2.5 or > 2.5
Hemophagocytosis of on bone marrow	Yes or no or unknowm
Platelet	< 110000 or > 110000

Immunomodulatory agents

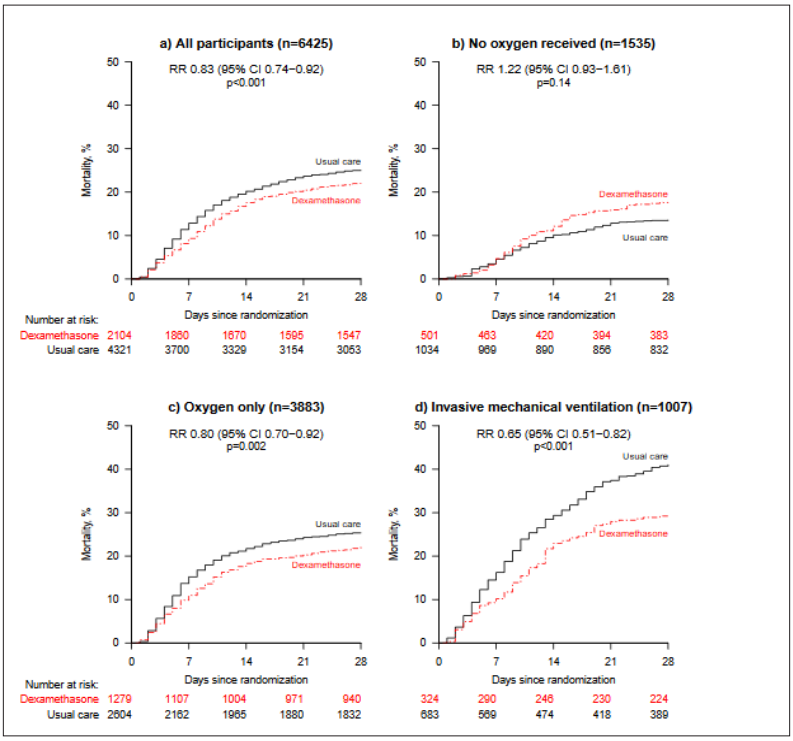
Immunomodulatory agents that directly target the key cytokines and inflammatory cascades involved in COVID-19 may help alleviate hyperinflammation symptoms in severe cases. They play important role in preventing progression to multiorgan dysfunction. Some of the potential immunomodulatory agents currently used in the treatment of COVID-19 are listed below:[7]

- **RAAS inhibitors**: Ang II effect inhibitor, it acts as anti-inflammatory and immunomodulatory agent.
- **Corticosteroids:** it is an anti-inflammatory agent, which help in prevention of extended cytokine response.
- **Hydroxychloroquine and Azithromycin:** Immunomodulatory agents with anti-inflammatory properties.
- **IVIG:** It provides non-specific passive immunity to viral infections.
- **Colchicine:** Shows anti-inflammatory activity by inhibiting tubulin polymerization plays an important role in mitigating the cytokine storm.
- **Convalescent plasma:** It can act as a passive immune therapy.
- **GM-CSF blockers:** It targets granulocyte-macrophage colony-stimulating factor to reduce inflammation.
- **Interferons:** Play an important role in reducing viral multiplication and modulating host immune system against viral infection.
- **Statin:** Helps in inhibiting myeloid differentiation primary response 88(MY D88) and (NF)-kB pathway to reduce inflammation.
- **Anti-TNF-α:** Helps in suppressing inflammation by blocking TNF receptor.
- **IL-1 inhibitor:** Acts by binding to IL-1 receptor to target cytokine storm.
- **IL-6 inhibitor:** Acts by binding to IL-6 receptor to target cytokine storm.
- **JAK inhibitors:** Targets cytokine storm by binding to IL-6 receptor.

Corticosteroids

The benefits of corticosteroids for managing COVID-19 related pulmonary disease is a matter of debate. A retrospective analysis involving 201 patients with COVID-19 pneumonia has noted substantial reduction in mortality with low-dose steroids.[8] Corticosteroids have been reported to modulate a variety of cytokines, thereby to manage cytokine storm-linked to SARS-CoV-2 infection.[9] Similarly, in recovery trial, dexamethasone was found to be beneficial for managing different categories of hospitalized patients and the benefits was found to be more for severe form of disease. The treatment reduced 28-day mortality in patients receiving oxygen and mechanical ventilation rather than patient not receiving respiratory support (Fig. 5).[10]

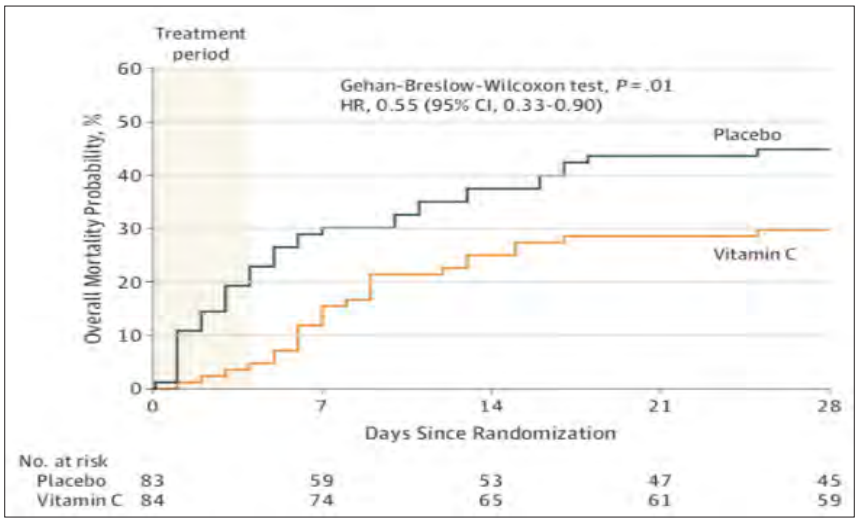
Fig 5: 28-day mortality in all patients(a) and separately according to level of respiratory support (b-d)



Vitamin C

Vitamin C can act as an immunomodulatory agent to improve function of immune cell and epigenetic immunologic modifications. It also induces oxidative stress and inflammation reduction. The CITRIS ALI randomized controlled trial demonstrated that the vitamin C infused patients demonstrated reduction in 28-day all-cause mortality when compared to placebo (46.3% vs. 29.6%) (Fig. 6).[11]

Fig. 6: All-cause mortality from 0-28 days in patients with sepsis associated ARDS



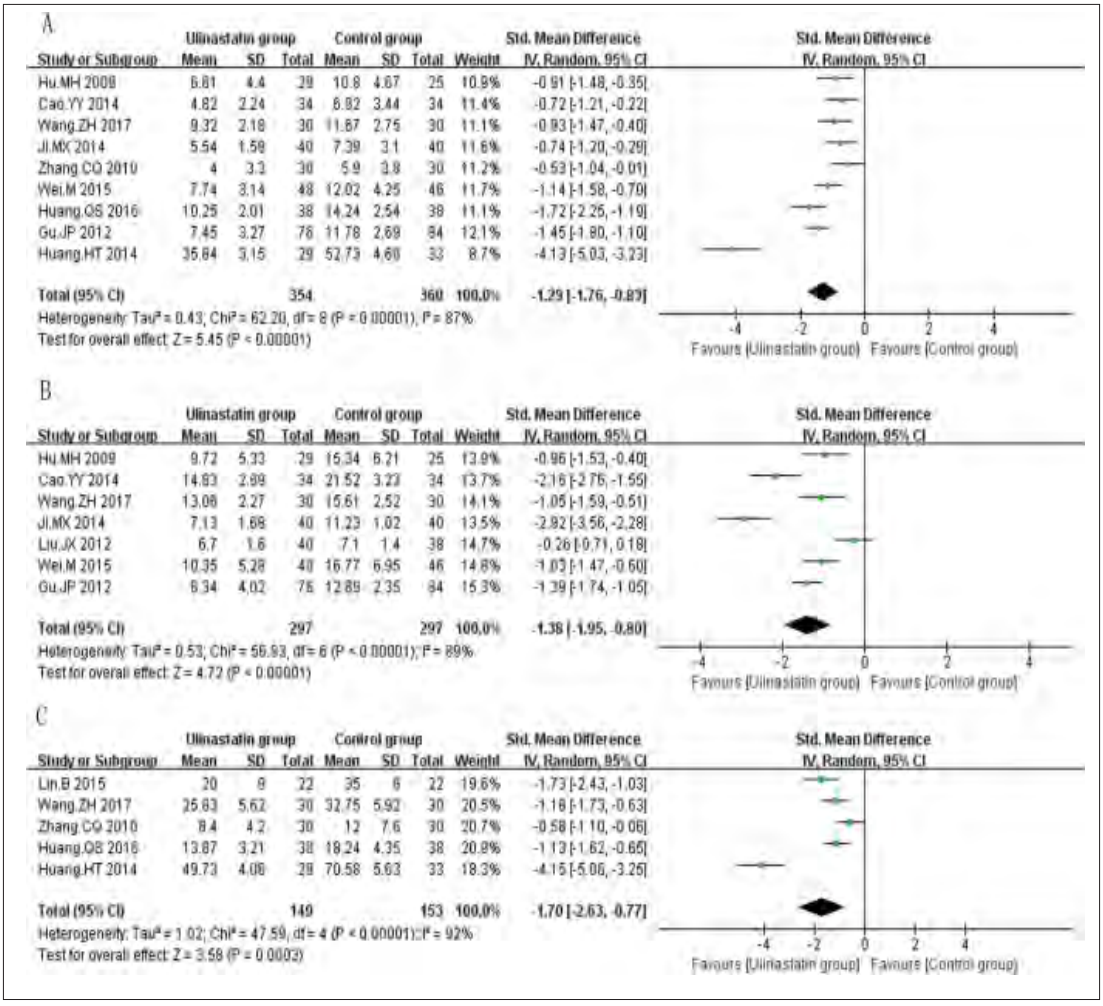
Heparin

The anticoagulation property of heparin helps in reducing disseminated intravascular coagulation, which in turn decrease the risk of end organ damage. Heparin also exhibits anti-inflammatory effects by binding to cytokines and inhibiting neutrophils and leukocyte migration. COVID-19 patients with markedly elevated D dimer and fulfilling SIC criteria taking anticoagulant therapy with low molecular weight heparin has demonstrated reduction in mortality.[12]

Serine protease inhibitors

Serine protease inhibitors act on the host cell receptor protease TMPRSS2, which is needed for binding of viral particle to ACE 2. Although, the likelihood of binding of viral particle is proposed to be reduced, there is lack of evidence to corroborate the mechanism. Several studies have shown the benefits of serine protease inhibitors in managing other forms of ARDS. A meta analysis have concluded on the benefits of ulinastatin, an acid-resistant protease inhibitor, in improving various outcomes such as reduction in mortality, shortening of mechanical ventilation, and ICU/hospital stay duration in ARDS patients (Fig. 7).[13]

Fig. 7: Metanalysis results of patients, a: duration of mechanical ventilation, b: intensive care unit stay, c: hospital stay



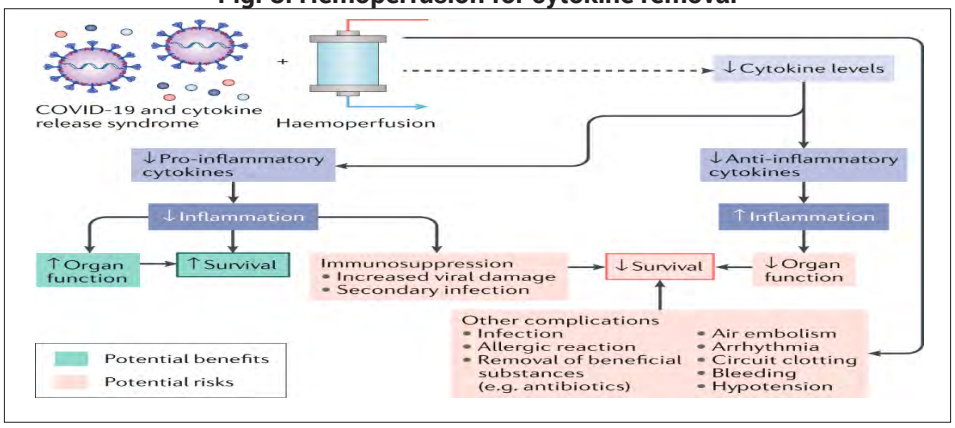
Convalescent plasma

It refers to the transfusion of antibody-rich plasma from the recuperated subjects to other infected patients, which may cause neutralization of viral particle by antibodies of the donor. Convalescent plasma helps in reducing the risk of inflammation and mortality (Fig. 9).[14] It is advisable to administer the plasma within 10 days of infection and the dosage recommended earlier by ICMR was 2 doses of 200ml over 24 hours. The recent press release by ICMR warns against the indiscriminate use of convalescent plasma therapy and suggested its use in necessary cases depending on clinician judgement.

Blood purification system

There is lack of evidence-based studies suggesting the success of blood purification system in managing COVID-19. Though several studies have evaluated the effectiveness, none of them have been translated to improve the survival rate of COVID patients. The purification process has been reported to decrease endotoxemia, and reduce cytokine levels and inflammatory markers. Some of the available blood purification systems include plasma exchange, plasma absorption, hemofiltration, high volume hemofiltration and cytosorb (Fig. 8).[15]

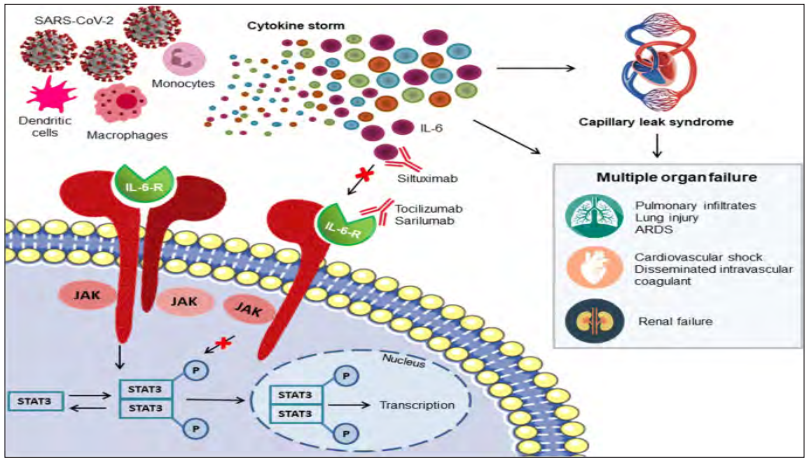
Fig. 8: Hemoperfusion for cytokine removal



Tocilizumab

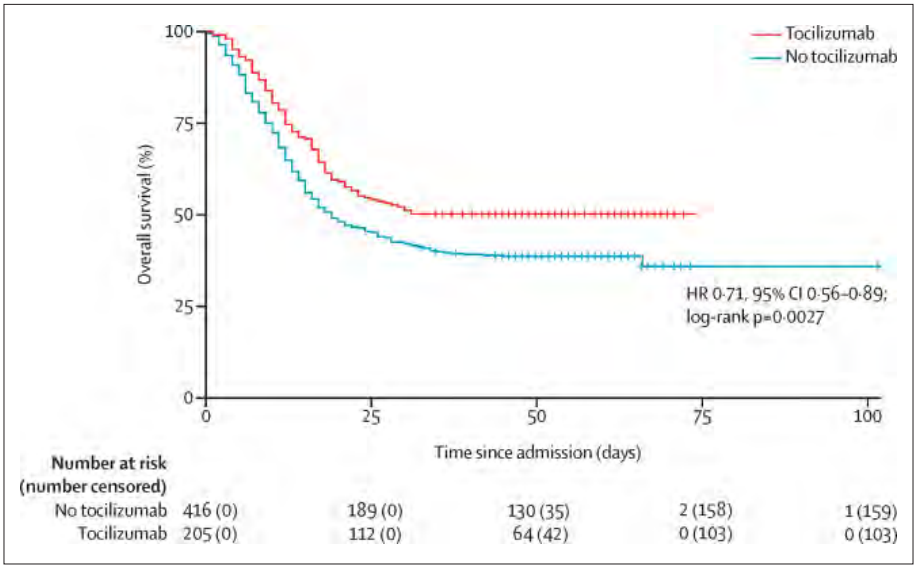
The drug acts by inhibiting IL-6 released as a part of cytokine storm. It prevents IL-6 binding to target receptor, thereby decreasing end organ or cellular impact of IL-6 on host cell (Fig. 9).[16]

Fig. 9: Mechanism of action of anti-IL-6 drug



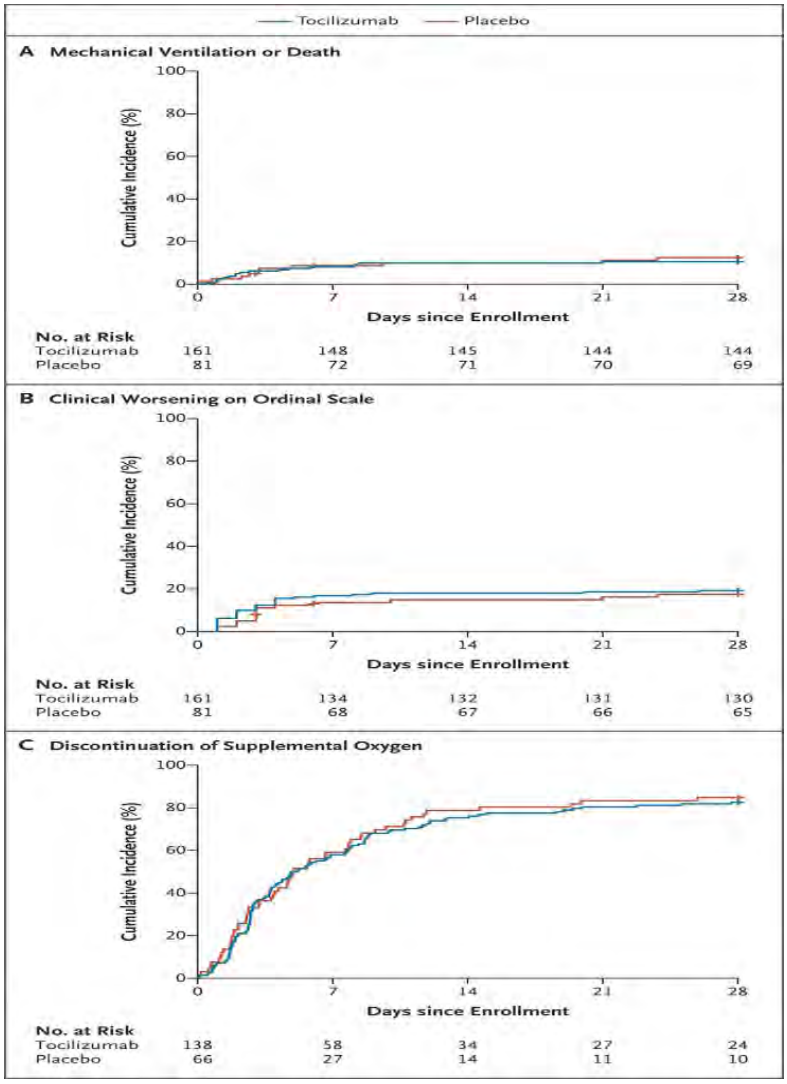
Initial literature data has demonstrated substantial benefits of tocilizumab in managing mild to moderate disease, decreasing the disease progression to severe stages, and reducing hospital-related mortality (Fig. 10).[17]

Fig. 10: Overall survival among patients who received tocilizumab



However, a study by Stone et al., conducted during the second half of the pandemic, demonstrated that the benefits of tocilizumab is extremely low in terms of mortality and secondary outcomes. Further clinical trials studies are needed to corroborate the efficacy of tocilizumab in treating hospitalized COVID-19 patients (Fig. 11).[18]

Fig. 11: Efficacy of tocilizumab on treatment outcomes



Other Immunosuppression agents

JAK Inhibitors namely baricitinib and neurokinin-1 antagonist such as tradipitant are the other immunosuppression agents under clinical investigation to decrease inflammatory response.

Immunomodulation: A double edge sword?

Modulation of cytokine response can be harmful. Prolonged immunosuppression by drugs like

corticosteroids and tocilizumab may increase the risk of serious side effects. Therefore, judicious of immunomodulators and selection of appropriate patient candidate are paramount. Well-designed clinical studies have not yet elucidated the beneficial use of immunomodulators targeting immune modulation based on levels of chemical mediators. Further studies are needed to corroborate the safety, efficacy, time / phase of intervention and use in clinical practice.

Conclusion

As in other forms of cytokine mediators-based interventions, there is no strong evidence to validate the safety and effectiveness of immunomodulating mechanisms and agents. Steroids can be recommended for managing mild to moderate disease, keeping in mind the contraindications and long-term complications. Tocilizumab may be beneficial in selected group of patients and needs to be validated through evidence-based trials. Clinician's discretion and experience play a major role in deciding the therapy.

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Fever in COVID 19: A Clinico-Epidemiological Perspective*

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Introduction

Since COVID-19 is still an emerging pandemic, there are several grey areas in understanding the epidemiological and clinical aspects of COVID-19. The present review focuses on the clinico-epidemiological perspective of fever in COVID-19, which may help in better understanding of the disease for preventing its community transmission and instituting effective clinical management.

Global and Indian scenario of COVID 19

The COVID pandemic has affected nearly all the countries, and as per WHO update of November 2020, more than 54 million individuals are afflicted globally. In addition, the death toll due to COVID has crossed more than 1.31 million. The current global scenario shows that cumulative number of cases was highest in the USA, India, Brazil, Russian Federation and France. Similarly, the 5 countries with highest cumulative number of deaths were the USA, Brazil, India, Mexico, and the UK (Fig. 1).[1]

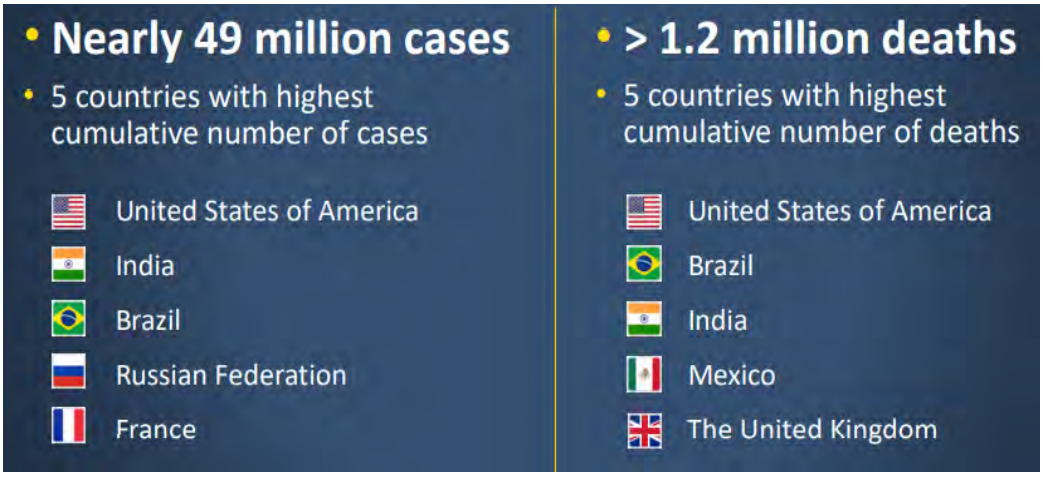

Fig.1: Countries with highest cumulative number of cases and deaths

In India, as of November 17, 2020, the total confirmed cases have crossed 88, 74, 290 with an approximate increase of nearly 30,000 cases per day. The estimate shows that the percentage of recovery from COVID -19 in the country was around 93% (N=82, 90,370) and the mortality rate was as low as 1.47% (n=1, 30,519) (Fig. 2).[2]

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*G.C.Surana oration lecture delivered on 20th November, 2020 at the 3rd National Virtual Conference of Fever Foundation organized from Bangalore.

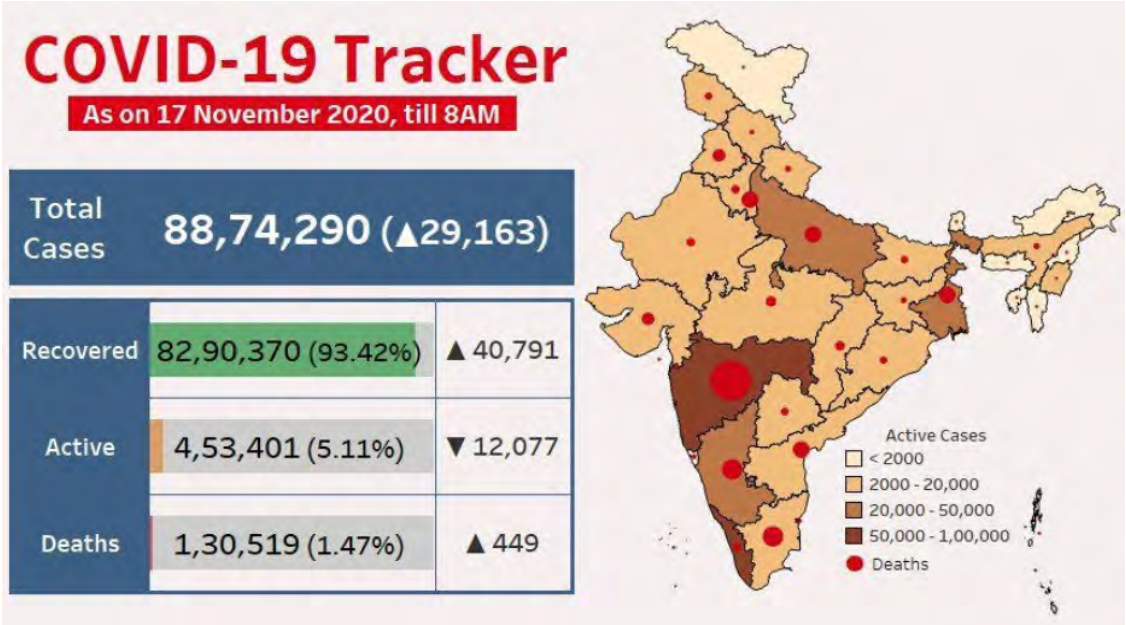
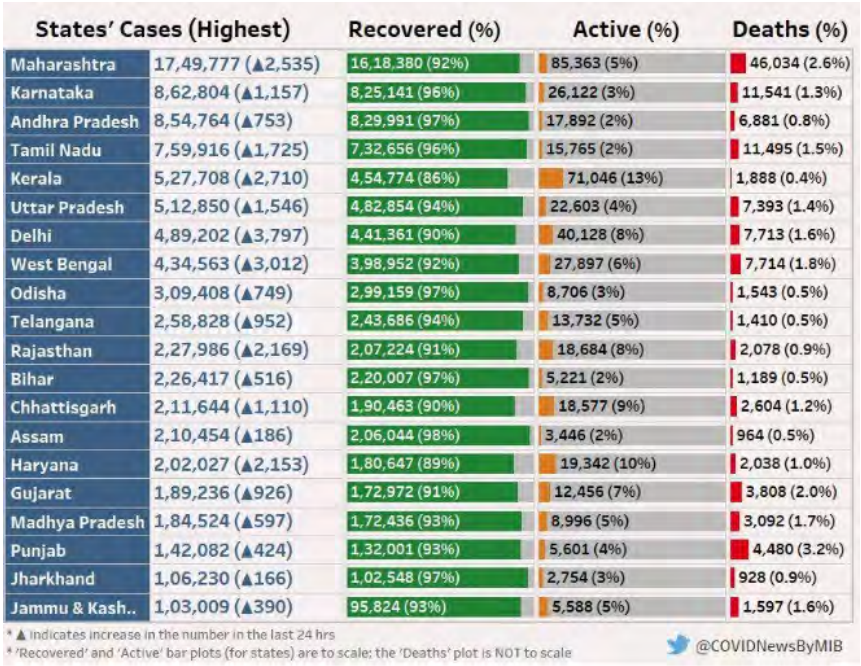


Fig. 2: India COVID scenario as on 17 November, 2020

The state-wise distribution shows that the cases were highest in Maharashtra (17, 49,777), followed by Karnataka (8, 62, 804,) Andhra Pradesh (8, 25,141) and Tamil Nadu (7, 59,916). A good surveillance is paramount for the effective management of the disease. Despite the high disease burden, the overall recovery rate was >90% in all the states (Fig. 3). The COVID-19 related mortality was more in the vulnerable groups i.e. elderly, obese, and those with comorbidities.[3]



States' Cases (Highest)		Recovered (%)	Active (%)	Deaths (%)
Maharashtra	17,49,777 (▲2,535)	16,18,380 (92%)	85,363 (5%)	46,034 (2.6%)
Karnataka	8,62,804 (▲1,157)	8,25,141 (96%)	26,122 (3%)	11,541 (1.3%)
Andhra Pradesh	8,54,764 (▲753)	8,29,991 (97%)	17,892 (2%)	6,881 (0.8%)
Tamil Nadu	7,59,916 (▲1,725)	7,32,656 (96%)	15,765 (2%)	11,495 (1.5%)
Kerala	5,27,708 (▲2,710)	4,54,774 (86%)	71,046 (13%)	1,888 (0.4%)
Uttar Pradesh	5,12,850 (▲1,546)	4,82,854 (94%)	22,603 (4%)	7,393 (1.4%)
Delhi	4,89,202 (▲3,797)	4,41,361 (90%)	40,128 (8%)	7,713 (1.6%)
West Bengal	4,34,563 (▲3,012)	3,98,952 (92%)	27,897 (6%)	7,714 (1.8%)
Odisha	3,09,408 (▲749)	2,99,159 (97%)	8,706 (3%)	1,543 (0.5%)
Telangana	2,58,828 (▲952)	2,43,686 (94%)	13,732 (5%)	1,410 (0.5%)
Rajasthan	2,27,986 (▲2,169)	2,07,224 (91%)	18,684 (8%)	2,078 (0.9%)
Bihar	2,26,417 (▲516)	2,20,007 (97%)	5,221 (2%)	1,189 (0.5%)
Chhattisgarh	2,11,644 (▲1,110)	1,90,463 (90%)	18,577 (9%)	2,604 (1.2%)
Assam	2,10,454 (▲186)	2,06,044 (98%)	3,446 (2%)	964 (0.5%)
Haryana	2,02,027 (▲2,153)	1,80,647 (89%)	19,342 (10%)	2,038 (1.0%)
Gujarat	1,89,236 (▲926)	1,72,972 (91%)	12,456 (7%)	3,808 (2.0%)
Madhya Pradesh	1,84,524 (▲597)	1,72,436 (93%)	8,996 (5%)	3,092 (1.7%)
Punjab	1,42,082 (▲424)	1,32,001 (93%)	5,601 (4%)	4,480 (3.2%)
Jharkhand	1,06,230 (▲166)	1,02,548 (97%)	2,754 (3%)	928 (0.9%)
Jammu & Kash..	1,03,009 (▲390)	95,824 (93%)	5,588 (5%)	1,597 (1.6%)

* ▲ indicates increase in the number in the last 24 hrs
* 'Recovered' and 'Active' bar plots (for states) are to scale; the 'Deaths' plot is NOT to scale

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Fig. 3: State wise distribution of COVID cases

The fever component of COVID-19

Fever is a common presentation of COVID-19, common cold, flu and allergies. At the beginning of the pandemic, WHO reported gradually increasing low-grade fever (≥100.4°F or 38°C) as a common symptom affecting up to 88% of those infected. However, the present scenario shows that up to 50% of individuals with COVID-19 are asymptomatic. It has been noted that the transmissibility of the infection from asymptomatics to close contacts at house and work place were very high.[4] But after a thorough probe it was found that a vast majority of them would have had transient fever or other mild symptoms or atypical manifestations, and as a result the 'truly asymptomatics 'was only around 20-30% and the other 20-30% were 'symptomatics'. It must be noted that since beginning of the pandemic, the COVID-19 surveillance has been conducted through testing the influenza-like illness (ILI) and severe acute respiratory infection (SARI).

There is substantial literature evidence to validate that fever triggers cellular mechanism and facilitates the immune response of the body. But the intake of antipyretics like paracetemol suppresses fever or may cause adverse effects, prolong and worsen the illness.[5] In patients who had contracted

COVID-19 infection, it has been noted that majority try to suppress the fever using paracetemol and other antipyretics. This may lead to development of infection-linked morbidities, hospitalization and ultimately death.

COVID-19 cases with more severe symptoms may carry a higher viral load of SARS-CoV-2 and greater transmission capacity. A study by Kumar et al. evaluated the transmission dynamics and epidemiology of SARS-CoV-2 in patients admitted to National Institute of Mental Health and Neuro Sciences (NIMHANS), Karnataka, India. The researchers have noted that viral transmission was significantly higher from asymptomatic cases and this may have major implications on testing policies. The study also highlighted the need to prioritize the testing and treatment for symptomatic subjects[6]. On the contrary, it has been reported that isolation and treatment of symptomatic patients has led to missing asymptomatic cases, and this is more hazardous in terms of public health perspective. These observations underscore the importance of testing the suspected individuals, instead of merely managing with antipyretics.

Fever may present at the beginning of the infection or appear later during the course of the illness. It can be persistent or intermittent for a few days. Hence, Government of India has implemented a uniform discharge policy throughout the country i.e. the patients admitted to a hospital, COVID care centre or managed in home isolation/home care should be 'fever-free' for 72 hours preceding the discharge from the facility. Many of these patients after discharge, as post COVID clinical condition have developed low-grade, intermittent fever along with other symptoms such as weakness, breathlessness, cough, and loss of appetite. The post COVID clinical syndrome is now receiving wide attention and post COVID care centres are being established all over the country[7].

Screening for COVID-19

Fever clinics have been established across India to screen for COVID-19 infection.[8] However, people were initially scared to visit these clinics due to the fear of testing positive and the subsequent process of - isolation, tracing and testing of contacts & quarantining them, seal down of residence & the surrounding area . However, over a period of time many of these public health actions have changed and as a result the individuals are now visiting these centres to get tested.
The screening devices used for checking for fever among the population have certain shortcomings. Hand-held thermal scanner is the most popular fever screening device used in public places like hospitals, offices, shops & malls, cinemas, metros stations, colleges, etc. However, the chances of false readings are high, as majority of these devices are not properly calibrated before its use. Besides such faulty screening leads to missing symptomatic cases and facilitating disease transmission. The digital thermometers are given to patients, as a part of the home isolation or home-care kit. Lack of knowledge of using such thermometers, and improper cleaning of the device by many may be leading to the spread of infection.[9]

The use of thermal body screening solutions in airports and big shopping arcades assists in rapid screening of the subjects for fever. Some of them are even equipped with auto-control of the gate to prevent the exit of those having fever or in some cases even those not wearing a face mask!

Conclusion

During the current pandemic situation, patients presenting with any type of fever should be suspected as having COVID-19 and managed on the basis of specified COVID-19 policies and protocols. Aggressive search for symptomatic cases and subjecting them to screening and treatment will be key to the containment of the pandemic.

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Illness beyond acute COVID-19

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Introduction

The COVID pandemic has claimed more than 1.34 million deaths and disease has affected 188+ countries worldwide. Acute infection of COVID-19 is characterized by active viral replication and initial host response with symptoms like fever, cough, dyspnoea, myalgia, headache, sore throat, diarrhoea, nausea vomiting, anosmia, dysgeusia, and abdominal pain.[1] The infection has been associated with the development of inflammatory syndromes and related clinical manifestations. The present review discusses post-COVID manifestations and related complications noted in certain post-COVID subjects.

Illness beyond acute COVID-19

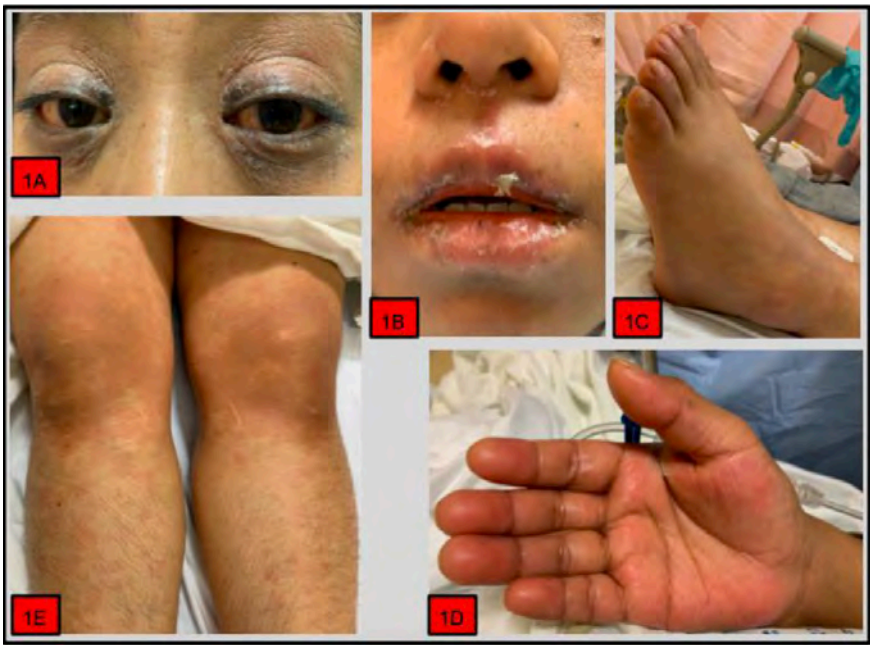
The development of post-acute hyperinflammatory illness or multisystem inflammatory syndrome (MIS) has been noted in certain patients after two weeks of COVID infection.[2] It is classified as C or A, depending on its occurrence in children or adults. This is marked by dysregulated host response and myriad of cardiovascular gastroenterological, dermatologic / mucocutaneous, respiratory, neurological and musculoskeletal symptoms. The week 4 of post-COVID infection is characterised by 'late sequelae' involving cardiovascular, respiratory, neurological, and psychological manifestations. The pathophysiological pathways are unproven and the viral and antibody profiles have not been characterized.

Multisystem inflammatory syndrome

As per the literature, only 10 cases of MIS-A have been reported worldwide. These patients had minimal respiratory symptoms or hypoxemia. It generally occurs 2-5 weeks after acute COVID-19 symptoms and mucocutaneous involvement like conjunctivitis, chapped lips, edema, rashes, and erythema are the common presentations. 3 Lab tests in suspected patients should focus on inflammation, hypercoagulability and organ damage. In children, anti-inflammatory/IVIG tests are helpful and prognosis is good with improved survival. Predominant clinical features noted in children include cardiac dysfunction, shock, abdominal pain, and elevated inflammatory markers, including ferritin, D-dimer, C-reactive protein (CRP), and interleukin-6.2

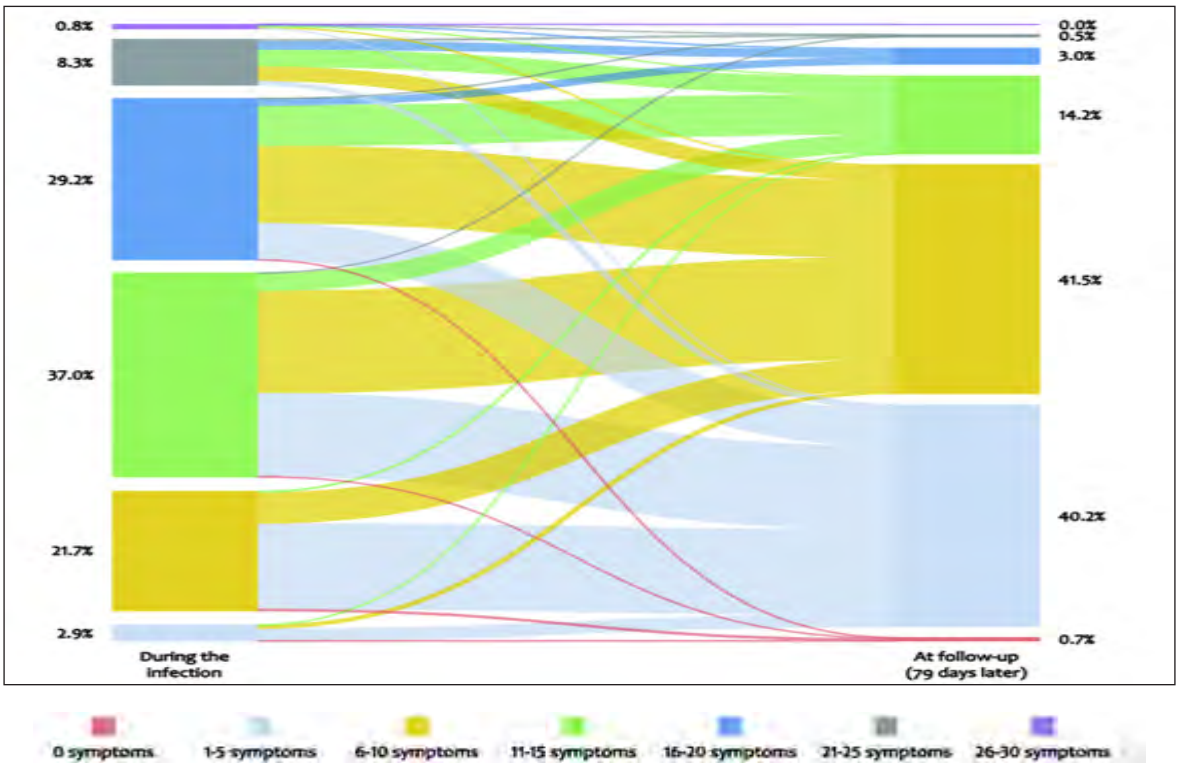
A recent case study by Sokolovsky et al. has reported the occurrence of a Kawasaki-like MIS-A in a 36-year-old woman. The disease presented as Kawasaki disease-like illness with serologic evidence of past COVID infection. The study highlighted the need for physicians to be cautious about inflammatory syndromes that mimic Kawasaki disease /Kawasaki disease shock syndrome, which may require prompt treatment with IVIG and steroids (Fig. 1).[4]

Fig. 1: Kawasaki disease-like features of MIS-A



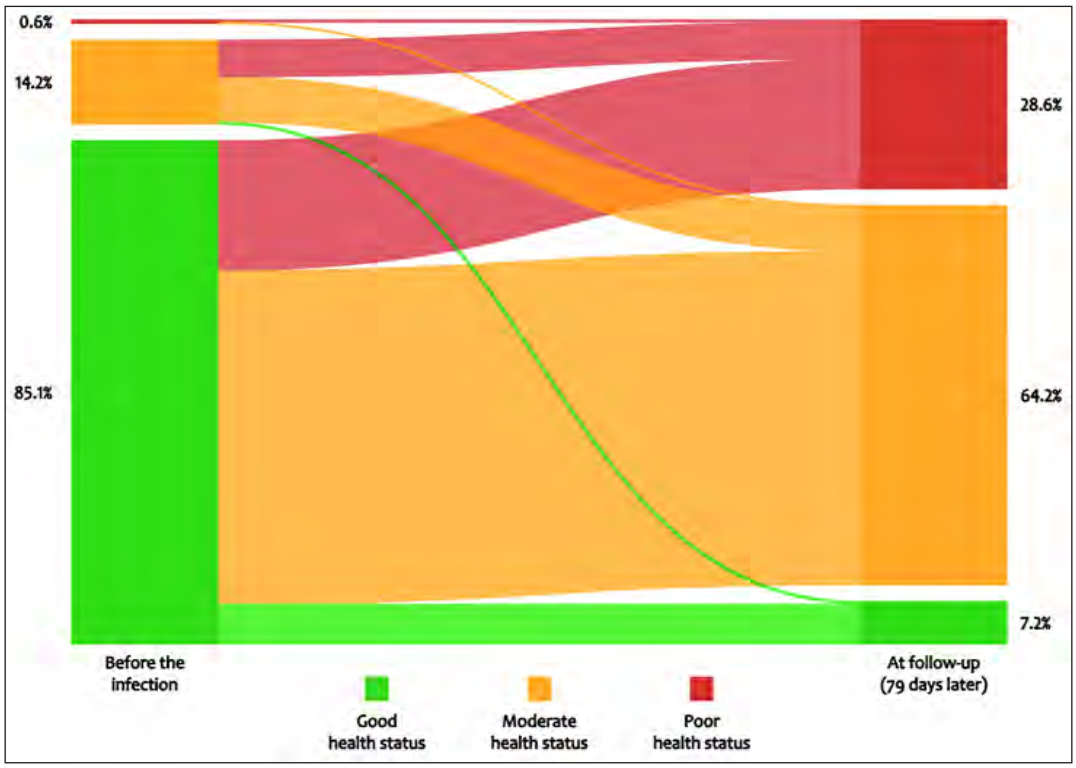
A survey carried out by Indiana university has reported fatigue, muscle ache, difficulty in breathing, headache, poor concentration as the common post COVID-19 symptoms observed. The survey involved a large cohort of previously hospitalised and non-hospitalised patients with confirmed or suspected COVID-19. The study has reported that the recovery was partial even after 3 months of symptom onset. The median number of symptoms noted was 14 (11–17) symptoms, and 97% of the participants had >5 symptoms (Fig. 2). [5]

Fig. 2: Prevalence and change in the number of symptoms during and 3 months after infection



Evaluation of prevalence and change in self-reported health status during 3 months noted that the post-COVID symptoms does not occur in isolation. The colour coding depicted in figure 3 denoted the occurrence of symptoms. The green colour indicated that most of the study participants had 11-15 symptoms. The follow-up done till 79 days showed that most of the patients had only 6-10 symptoms (shifted to yellow color code). This finding showed that a significant portion had only 1-5 symptoms at the end of follow-up, with a small percentage still having 11-15 symptoms.[6] Prior to the infection, most of the subjects had good health status, but post-COVID health status became moderate or poor.

Fig.3: Prevalence and change in self-reported health status during 3 months of evaluation



Post COVID-19 syndrome: Definition

Some patients continue to experience symptoms related to COVID-19 after acute phase of infection[7] Persisting symptoms have been defined by the presence at day 30 or day 60 of at least 1 of the following: weight loss >5%, severe dyspnea, chest pain, palpitations, anosmia, headache, skin changes, arthralgia, myalgia, digestive disorders, fever or using sick leave.[8] Long COVID, post-COVID syndrome, post-acute COVID-19 syndrome, long-haulers are the synonyms for post-COVID-19 syndrome.

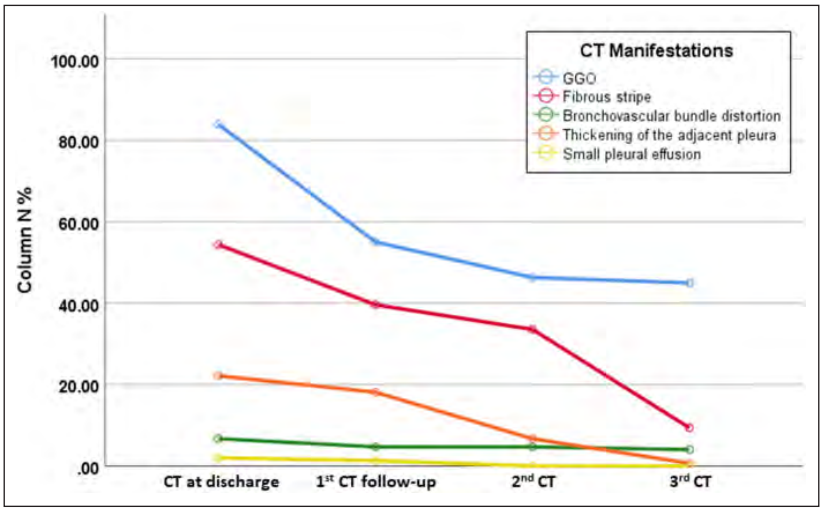
Structural lung damage

The following structural lung damages have been noted in patients post COVID-19 infection. However, it is not known if the damages are transient / reversible or progressive.[9],[10]

- Bronchial thickening and bronchiectasis
- Diffuse alveolar damage
- Lung fibrosis [direct injury / as a complication of ARDS]
- Pleural thickening and pleural effusion

A cohort study in Wuhan using spirometry showed that most of the subjects post COVID demonstrated significant decrease in diffusion of lungs, and restriction of lungs was the second common pulmonary sequalae (Fig. 4).[11] These pulmonary sequalae caused cough and shortness of breath in post-COVID-19 patients.

Fig.4: Dynamic changes of chest CT manifestation



A case series by Vechi et al. reported thromboembolic events as a potential complication of mild COVID-19 and its manifestation later in the disease course. This is a very common manifestation occurring in many post-COVID-19 patients. It can occur beyond 2 weeks of hospitalization and in mild recovered cases. Exact factors associated with the occurrence of thrombolytic disease are unknown.[12]

Lung damage may be significant in some patients leading to shortness of breath/cough. The post-COVID cough can occur due to reasons. It is imperative to identify the underlying cause of the cough to decide on the treatment approach. The respiratory and non-respiratory causes are briefed in table 1.

Table 1: Respiratory and non-respiratory causes of post-COVID cough

Respiratory	
• Post viral cough • Upper airway cough syndrome • Asthma • COPD • Respiratory tract infections [URTI/ LRTI/ pneumonia]	• Bronchiectasis • Lung fibrosis • Lung cancer • Aspiration pneumonitis • Pleuritis/ pleural effusion • Cough hypersensitivity syndrome
Non-respiratory	
• GERD and laryngopharyngeal reflux • Drugs • Cardiac [heart failure]	• Foreign body aspiration • Post infectious vagal syndrome • Pericarditis • Psychogenic

Red flag signs

Red flag signs to be considered in post-COVID patients are listed below: [13]

- Hemoptysis
- Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
- Hoarseness
- Systemic symptoms
- Fever; weight loss
- Peripheral edema with weight gain
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough
- Adults aged 55-80 years who have a 30 pack / year smoking history and currently smoking or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night trouble swallowing when eating or drinking

Cardiac inflammation

Cardiac inflammation including myocarditis may appear in post COVID-19 patients. A case-study by Sardari et al. concluded that myocarditis may occur due to residual myocardial inflammation as a result of COVID-19, and there is a chance for overlooking cardiac involvement during pneumonia. The study reported the case of a 31-year-old who was positive for SARS-CoV-2 through RT–PCR and having bilateral ground-glass and consolidative opacities mostly in the right lower zone. Three weeks after discharge, he presented with dyspnoea on exertion and low-grade fever. Cardiac magnetic resonance showed oedema/inflammation in the mid inferoseptal and inferior wall, and the late gadolinium enhancement showed subepicardial fibrosis in the mid inferior wall. These clinical and imaging features were suggestive for active myocarditis.[14]

A cohort study involving 100 patients recently recovered from COVID-19 has highlighted the need for ongoing investigation for the long-term cardiovascular consequences. The cardiac magnetic resonance imaging revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%). This was found to be independent of pre-existing conditions, severity and overall course of the acute illness, and the time from diagnosis.[15]

Renal manifestations

There are reports of renal manifestations such as collapsing glomerulopathy and renal injury in post-COVID patients. Histopathologic findings also corroborated the presence of viral particles in tissues. A case study by Peleg et al. reported that a significant proportion of the population with West African ancestry may be at risk of developing kidney injury due to collapsing glomerulopathy, as the COVID-19 pandemic cases are increasing in African continent. The study has presented the case of a 46-year-old West African man who developed severe acute kidney injury requiring renal replacement therapy due to collapsing glomerulopathy in the context of COVID-19 infection.[16]

Neurological manifestations

Analysis of social media data conducted by Banda et al. reported that post-COVID patients had long-term symptoms like pain, myalgia, anosmia, amnesia, tinnitus, and other features suggestive of neurological involvement.[17] A correspondence published by German researchers have reported the persistence of olfactory dysfunction in patients following the recovery from COVID-19.[18] The study followed up 50 patients who presented to the ENT OPD (mean age 43.2 years). All the subjects were RT-PCR positive and had recovered at least 3 weeks before the current visit. The key findings were as follows:

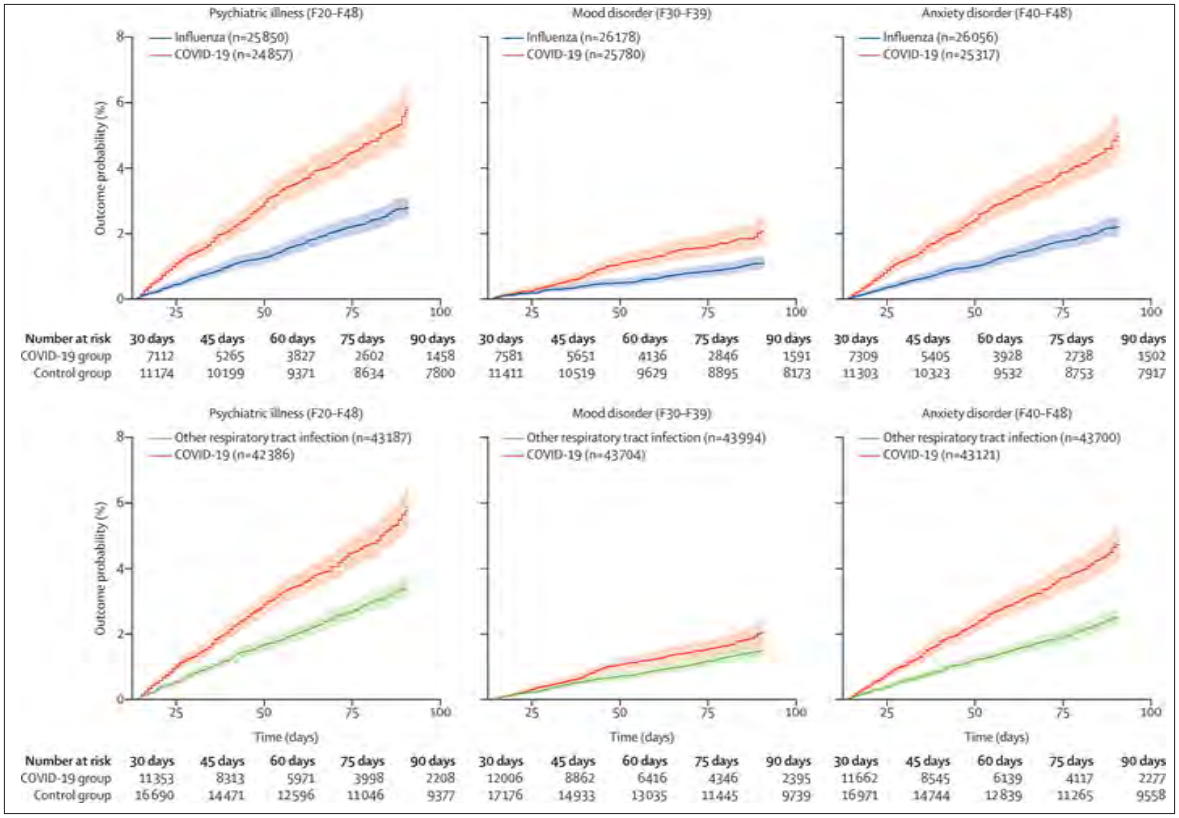
- 94% had lost smell due to acute COVID-19 infection
- 38% of patients still complained of olfactory impairment
- 52% had hyposmia during objective testing
- No difference in groups in terms of patients' age, sex, and smoking history

A prospective evaluation of non-hospitalized subjects has reported the occurrence of olfactory and gustatory dysfunction in 83% and 89% of subjects respectively. The study has also observed that corresponding 10% to 15% of the patients had only partial improvement during the time of study.[19] Literature studies have also noted that psychiatric and other system manifestations may have an adverse impact on post-COVID-19 patients leading to poor health status.

Post-COVID-19 psychiatric manifestations

An electronic health record network cohort study using data of 62, 354 US patients diagnosed with COVID-19 has evaluated whether a diagnosis of the infection (compared with other health events) was associated with increased rates of subsequent psychiatric diagnoses, and whether patients with a history of psychiatric illness are at a higher risk of being diagnosed with COVID-19.The study has concluded that subjects who had COVID-19 has higher chances of developing psychiatric illnesses such as mood and anxiety disorders (Fig. 5).[20] Other less commonly reported manifestations noted in post COVID patients are rash, dry eyes, and difficulty in sleeping. [21]

Fig. 5: Comparison of onset of first psychiatric diagnoses after COVID-19 diagnosis with influenza and other respiratory tract infections



Approach to post-COVID-19 patients

Since multiple systems are affected, it is ideal to adopt holistic approach for managing post-COVID-19 patients. It is mandatory to collect details of patient history, comorbidities and socioeconomic circumstances. Required tests such as blood test, ECG and imaging should be done according to patient's symptoms. Appropriate measures should be taken to manage the patient's comorbidities such as diabetes, hypertension etc. The treatment should focus both on medical and self-management. Medical management should be based on symptoms present and self-management should emphasize on different aspects of life. If required, the patient should be referred for specialist care. Since mental health deterioration is one of the main components in post-COVID recovery, specialist care should be sought in necessary patients. Finally, socio-cultural and financial supports should also be provided. [20]

Conclusion

COVID-19 can lead to symptoms post 2 weeks of disease onset and some subjects have reported long-term persistence of symptoms. Lung damage and cardiac inflammation including myocarditis may be prominent in post-COVID-19 patients. Renal manifestations like collapsing glomerulopathy may be seen. It is also paramount to watch out for post-COVID neurological syndrome, olfactory/ gustatory dysfunction, and psychiatric manifestations. An integrated multidisciplinary approach to manage post COVID-19 patients is highly warranted.

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Mental health in the time of COVID-19

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Introduction

The emergence of COVID-19, with its rapid spread, has exacerbated anxiety in populations globally, leading to mental health disorders in individuals. The pandemic has not only raised concerns over general public health, but has also caused a number of psychological and mental disorders. The present review appraises mental health scenario in India, and challenges and interventions related to the management of metal health problems in vulnerable groups and health workers.

Mental health scenario in India

According to a 2015-16 survey by the National Institute of Mental Health and Neuro-Sciences (NIMHANS) Bengaluru, India, nearly 13% of Indian population (150 million) suffers from some form of mental disorder.[1] In contrast, fewer than 30 million individuals were getting interventions and this is a huge treatment gap. If left untreated the ramifications are longitudinal and trans-generational, adding to the country's social and economic burden. Over the last few years, the Indian government has spent only 0.05% of its health budget annually on mental health improvement, much lower than the average expenditure of other low-income countries. Moreover, there is a dearth of mental health professionals in the country to meet the increasing mental health needs. The number of registered psychiatrists in India is estimated to be around 5000/6000 (required: 13,000 to 15,000) and as for other mental health professionals, we have only 1000 clinical psychologists (required: 20,000), 900

psychiatric social workers (required: 35,000), and only 1500 psychiatric nurses (required: 30,000). To give perspective India has only 1.93 mental health workers for every 1 lakh people (2017 figures). According to the WHO estimations, by 2020, around 20% of the people in India will suffer from mental illness.[2] India is dubbed as the capital of suicide in Southeast Asia and nearly 2.2 lakh suicides is estimated to occur per year in the country. [1]

Need of the hour

Considering the unmet mental health needs, implementation of the following interventions on the field of mental healthcare is inevitable:

- Robust psychoeducation to combat lack of awareness and stigma.[3]
- A multi-pronged approach to reduce the pervasive stigma associated with mental health disorders through various media campaigns.
- Dealing of psychological issues more sensitively in films and television series through social media campaigns.
- Integration of mental health system with general health framework, i.e. strong liaison among general physicians, specialists, psychiatrists and psychologists. [4]
- Collaboration between stakeholders at grass root and community levels, i.e. providing large scale psycho-social crisis interventions to state and central agencies, academic institutions, medical collages and religious groups.[5,6]
- Developing a strong public health system and policy reforms, which should provide actionable and scalable ideas and innovations.[6] The existing ASHA model needs to be scaled up to be more scalable and gender agnostic.[7,8]
- Incorporation of mental healthcare in future disaster management plans.

Challenges in therapy and management during a pandemic

The 3 most common fears confronted by residents of a pandemic-inflicted country are fear of illness, fear of uncertainty, and fear of death leading to anxiety disorders like adjustment disorder, generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD).[9] Non-bereavement related losses due to abrupt changes in daily life leads to uncertainty and loss of agency over one's life. Loss of social connection, loss of jobs, disturbance in life, economic instability etc. also lead to mental instability.[10]

In order to address these challenges in the acute phase, triaging is conducted to assess the severity of distress in both the worried well and those with pre-existing mental health issues (more severe for those with OCD, clinical depression and addiction).[11] It is imperative to focus more on the psychological first aid, to provide emotional support to identify existing resources, and build emotional agility and resilience. This may help the patient to identify and acknowledge emotions, shift perspective by zooming out and focusing more on what's in their control.

In patients with suicidal ideation and increased tendency to self-harm,[12] a much more robust gate-keeper training should be provided with crisis and safety plan to overcome the acute distress. Generally it has been noted that suicide peaks between 12 am and 4 am, highlighting the need of a 24hr helpline services. India currently has only around 40-50 suicide helpline services and of these

only 5-8 that work 24/7. It would be useful to adapt technology like artificial intelligence and machine learning technologies that services such as Crisis text line.org that operate in the US use to address the problems of high-risk individuals by highlighting some of the messages with words like suicide, kill, hopeless etc.

Challenges in managing vulnerable groups

- Psychoeducation, reassurance and continuous support should be given to the vulnerable groups who have tested positive, those in isolation, those who have lost loved ones due to COVID-19, and patients struggling with post COVID fatigue and depression.[10]
- Women are prone to show increased anxiety and depression due to juggling multiple responsibilities and increase in intimate partner violence.[13] Orissa police has teamed up with state crime bureau to implement a phone-up program to call and check out people with previous record of domestic violence. India would do well to emulate the French government's initiative of housing domestic violence victims in hotels financed by the government and provide pop-up counselling centers in grocery stores. The French and Spanish government unveiled a unique program to protect women who are victims of domestic abuse. All they had to do was walk up to a pharmacy and say 'Mask-19' to indicate an incident of domestic abuse and the pharmacist would then alert the authorities.[14]
- Among children, increase in restlessness, anxiety and acting out due to loss of social connection, online classes, and curtailing of play time being have been noted. Cyber bullying and violence at home are also some of the challenges faced by children.
- The problems noted in senior citizens include loneliness, helplessness, paranoia, suicidal ideation due to restriction in social connection. They also have had to depend on neighbours for their grocery needs etc because of restricted movements outside of their homes. With some not being technologically savvy the dependence on others has increased for buying many essential items. The usual social support structures of places of worship, meeting with friends, walks etc are no longer available to them because of the pandemic.
- Migrant and daily wage workers have been struggling during and after lock down for their daily food and livelihoods.
- The pandemic crisis has magnified the inequalities among sexual minority groups and access to healthcare has become a concern for them due to social stigma and deprioritization of their medical treatment.

Healthcare workers and pandemic challenges

Presently, frontline health workers namely doctors, nurses, technicians and ambulance drivers are the most vulnerable group. Multiple studies conducted by *Lancet* have reported the long-term effects of the SARS out break and resulting quarantine among healthcare workers. It has been found that the quarantined hospital staff reported highly depressive symptoms up to three years after quarantine. The following health concerns are also found among healthcare workers.[16]

- Increased stress and anxiety because of long shifts, physical exhaustion, mental burnout, emotional exhaustion and feeling of depletion.[17]
- Burn-out leading to low mood and depression often resulting in self-medication and addiction.
- Fear of infecting family.[18]

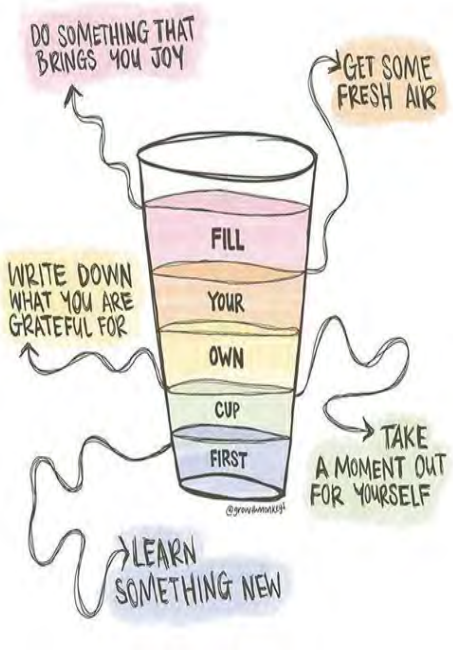
- PTSD, vicarious trauma and compassion fatigue are common among physicians who are posted in remote or underserved areas. The cumulative risk on practice can also lead to these conditions.[19]
- Some of the wide range symptoms experienced by health workers are as follows:
    - Emotional symptoms like grief, anxiety, sadness, irritability, anger and inability to focus.
    - Behavioral symptoms like isolation, increased substance abuse, insomnia, erratic eating habits and avoidance.
    - Physiological symptoms like heartburn, headaches, unexplained rashes and ulcers.
    - Cognitive symptoms are cynicism, negativity bias, difficulty in concentration, decision making, and intrusive thoughts about trauma sometimes leading to medical errors.
    - Spiritual symptoms are loss of hope, decreased sense of purpose, nihilistic tendencies, feeling disconnected from the world and moral distress.
- Risk of suicide is highest among doctors as compared to other professionals.[20] Personal, professional and institutional stigma are often the obstacles to seeking help.

Simple strategies to improve mental health

Simple strategies that can be incorporated in day-to-day routine to stay healthy and maintain mental wellbeing are briefed below (Fig.1):

- Peer support groups for debriefing and problem solving can help to reduce anxiety and stress.
- Use of helplines where anonymity is maintained – NIMHANS, IMA's Psycho Social Counseling helpline, Green Oak Initiative, D for D (IMA), Swaasthi.[21]
- Finding small ways to look after your well-being like anticipating small pleasures like a good book, a favorite show, a good meal etc.
- Use of Apps like Calm, Headspace, The Mindfulness App, Portal, and10% Happier.[22]
- Acknowledge, normalize and accept the emotions.
- Connect to physical surroundings whenever there is a feeling of anxiety.
- Remind oneself of the meaning and purpose of work.
- Start the day with a quick body scan, allow space for feelings, try to be curious and nonjudgmental and be present to whatever shows up.
- Check oneself daily and pay attention to physiological hyperarousal.

Fig.1: Strategies to improve mental health



Conclusion

The alarming situation of mental disorders in India poses a major social and economic burden to the country. The India government has to give more priority in providing facilities to improve the mental health of people who are affected during and after COVID -19 and lockdown. The health workers who are doing long working hours and quarantined for longer time need good support systems. They also need to undergo a self-evaluation to identify their own strengths and resources, allow space for their feelings leading to better emotional regulation and seek medical and mental health care, whenever necessary.

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COVID:
New normal

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Introduction

The pandemic has changed the way of working, learning and interaction throughout the world. In addition, due to the implementation of social distancing guidelines, people have adapted to a more virtual existence, both personally and professionally. The reduction in the rate of infections in some hard-hit areas demonstrates the early signs of recovery. Considering the uncertainties in economy and impact on various business sectors, states and cities have starting reopening of businesses, public areas and religious and educational institutions.[1] However, eradication of the virus hinges upon the availability of a safe vaccine. Although people are trying to resume work, school and a normal life, there will be a continued risk of infection, until the availability of a safe and effective coronavirus vaccine. The pandemic has also changed the people's approach to healthcare.

What is the new normal?

Preventing large indoor gatherings, limiting non-essential travel, and restricting, closing or restructuring business and school are some of the currently adopted measures to prevent COVID-19. The 3Ws to be followed and 3Cs to be avoided for the prevention of COVID -19 transmission are listed below:[2]

3Ws to be followed	3Cs to be avoided
• Wear a mask	• Closed space with poor ventilation
• Watch you distance	• Crowded spaces with many people nearby
• Wash your hands	• Close contact setting such as close-range conversation

New normal: Definition

It is a state to which society, economy etc. settles following a crisis, when this a change in the situation that prevailed prior to the start of the crisis.[3] The term has also been used in relation to the financial crisis of 2007-2008 and the aftermath of the 2008-2012 global recession.

The need of 'new normal'

COVID 19 is a long-term threat to the public and the world is nowhere near acquiring herd immunity. It is the most disruptive infectious disease threat that would has faced in this century.[4] The impact of each pandemic on the world economy is massive, thereby raising concerns on its revival in the post-COVID era. As per the estimate, the global economy impact may be between USD 5.8 trillion and USD 8.8 trillion.[5] Less economic devastation has been observed in countries with strong public health system, which helped to control the disease transmission and reduce mortality. However, the increased COVID-19 risk of transmission will not end with vaccine. The global health community has been warned about the inevitable emergence of new pathogens, which may constitute a major public health threat. The comprehensive public health responses needed during a pandemic are reduce spread, stop cluster formation, protect on-going healthcare and the use of data-driven progress to reduce transmission. Considering the futures risks for newer pandemics, preparedness for the pandemic is the smarter move.[6] Following the incidence of Spanish flu and plague, the importance of wearing PPE/ face masks and social distancing were highlighted. Individuals' reluctance to accept the 'new normal' and not following the controlling measures are the primary reasons for wider spreading of infection and its emergence as a pandemic. Most of the pandemics can be controlled by following the 'new normal'.

The definitions put forth by WHO for suspected cases are as follows:[7]

- Acute onset of fever and cough OR ≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status.
- Residing or working in an area with high risk of transmission, residing or travel to an area with community transmission or working in a healthcare setting.
- Patients with severe acute respiratory illness (acute respiratory infection with history of fever or measured fever ≥ 38°C and a cough; onset within last 20 days; requires hospitalization.

New normal 1- significance of history collection (either in virtual or real)

During the pre-COVID time, the history collection process conducted by the physician was very poor,

and the diagnosis of diseases was made mainly on the basis of signs and symptoms. In addition to the clinical signs and symptoms, it is important to consider epidemiological history, sick contact history and risk factors to confirm COVID (Fig. 1).

Fig. 1: Information to be documented as a part of history collection

Travel destination (including urban/rural)
Reason for traveling
Dates of travel & time between return and presentation
Sexual history and other risk behaviors
Any pretravel health advice obtained and precautions taken against disease
Viral hemorrhagic fever assessment for patients presenting with fever

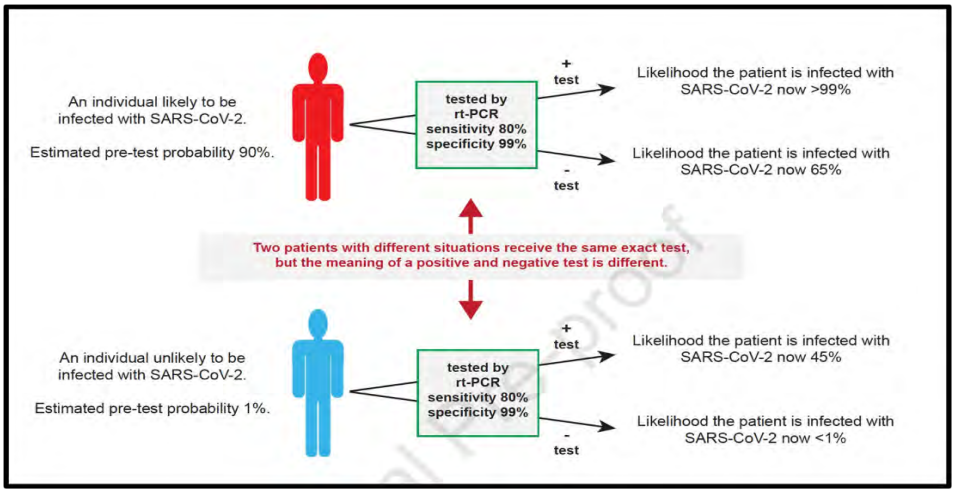
In the present scenario, it is paramount to collect the following details of infectious disease exposure history:[8]

- Immunization: Vaccination status (age appropriate, co-morbidities, travel etc.)
- Medication: ART, immunocompromising medication; drug exposure and allergies, prophylactic medication
- Dietary: Consumption of specific foods (unpasteurized milk and street food etc)
- Sexual: Partners, practices, protection, past STI history.
- Occupation/others: current or previous work exposure, incarcerations, homelessness
- Animal/ arthropod/activities: Animal exposure, tick/mosquito bites, hiking, kayaking, daycare, hunting etc.
- Place: Travel history, place of residence, proximity to livestock/ animal farms, rural/urban etc.
- Sick contact: Similar illness in household members, past ID history in family member

New normal 2: Interpreting the tests with clinical diagnosis

Instead of relying on blood cultures, antibody test or antigen test; the new normal test is PCR test-based diagnosis for COVID-19. According to WHO interim guidance on diagnostic testing, routine confirmation of SARS-CoV-2 infection should be based on the detection of unique sequences of RNA by nucleic acid amplification tests such as RT-PCR (Fig. 2). Presence of one or more negative results should not rule out the possibility of SARS-CoV-2 infection. Interpretation of the tests along with this clinical judgement is important to avoid false positive or negative diagnosis. Factors potentially leading to negative result in an infected individual are poor specimen quality, timing or location of specimen collection, inappropriate specimen handling, and inherent technical reasons.[9]

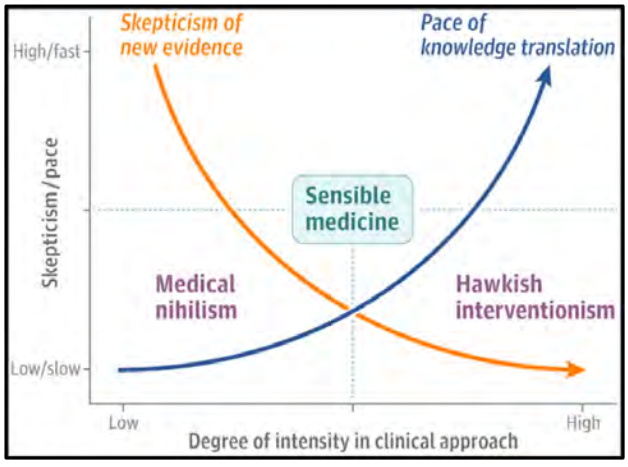
Fig. 2: Significance of PCR test in diagnosing SARS-CoV-2 infection



New normal 3: Follow sensible medicine

Following sensible medicine is the new normal for managing COVID-19. It is a treatment approach that seeks a balance between the strength of evidence and the pace of knowledge translation. It can adopted by extrapolating the clinician's knowledge based on the clinical experiences of similar situations, and reducing unnecessary interventionism by focusing and relying on scientific rigor (Fig.3).[10]

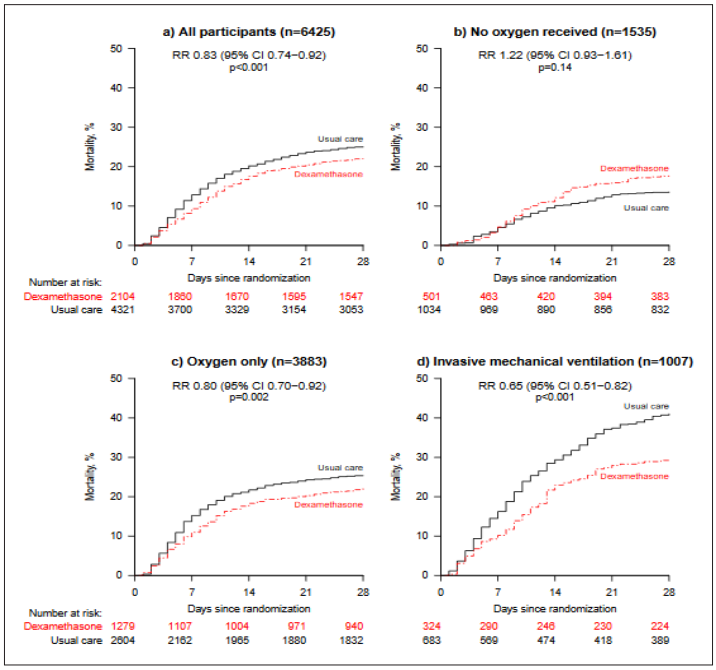
Fig. 3: The model of sensible medicine



Steroid is a life -saving drug if the patient is intubated, mechanically ventilated or on high oxygen flow. However, the value of glucocorticoids for managing COVID-19 infection is widely debated. A preliminary study by RECOVERY collaborative group has concluded on the benefits of dexamethasone in reducing 28-day mortality among patients who were receiving either invasive mechanical ventilation

or oxygen alone at randomization, but no such benefits was found in those receiving no respiratory support (Fig.4).[11]

Fig. 4: The effect of dexamethasone on 28-day mortality



New normal 4: Basic infection prevention

Healthcare workers are at high risk for occupational transmission of pathogens. This includes physicians, nurses, pharmacists, technicians, morticians, dentists, students, contractors, attending clinicians, public safety workers, emergency response personnel, healthcare waste workers etc. As per the estimate, 3 million healthcare workers are exposed to bloodborne pathogens each year and > 90% of infections occur in developing countries. As per the latest press release by IMA, 515 doctors who had COVID-19 patients have been succumbed to the infection. It is imperative to adopt basic infection control as a part of routine clinical practice. The aim of adopting standard precautions is to prevent transmission of pathogen by considering that blood and other body fluids are potentially infectious.[12]

New normal 5: Ventilation and Vaccination

Improving the ventilation of houses and healthcare settings is advocated to control airborne infections.[13] Considering the primary exposure to infected patients and infective materials, immunoprophylaxis through vaccination is highly recommended for healthcare workers. As per the Government of India's COVID vaccination plan 1 crore frontline healthcare workers have been selected to be the first recipients of vaccination.

Conclusion

"Never again. We should never be unprepared for something as catastrophic as what we are going through now." Dr Anthony Fauci, the US infectious expert and immunologist.[14]

Creative solutions are needed to strengthen and sustain core capabilities of public health system. The effective response plan for future pandemics should focus on:

- Prevent and reduce likelihood of outbreaks – natural, accidental or intentional.
- Detect threats early to slow or stop spread of outbreaks.
- Respond rapidly and effectively through government services and public-private sector partnerships.

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Telemedicine for COVID: Virtually perfect?

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Preamble

Telemedicine is now emerging as an important tool for providing convenient care and services in various fields of medicine. This is particularly beneficial for patients in remote locations with limited access to standardized healthcare services. The following description has been given by WHO to define the term 'telemedicine'.

'The delivery of health care services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities.[1]

In earlier days, telemedicine was not legal to prescribe medicine using any virtual technology platform. On March 25, 2020, the Board of Governors formed by the Health Ministry to regulate practice of modern medicine, has passed an amendment to the Indian Medical Council Regulations, 2002, to legalize the practicing of telemedicine.

The relevant part of the amendment is given below:[2]

3.8.1. *Consultation through Telemedicine by the Registered Medical Practitioner under the Indian Medical Council Act, 1956 shall be permissible in accordance with the Telemedicine Practice Guidelines contained in Appendix 5 (of Code of Conduct).*

This could be considered as a watershed moment in Indian healthcare sector, as the telemedicine helps to improve timely access to appropriate interventions and affordability, thereby to reduce the burden on hospital care settings.

Role of telehealth in managing the pandemic

During the current pandemic times, telemedicine is being adopted by more healthcare practitioners to provide remote care access and it is bridging the gap between clinician and patients. The key benefits of telemedicine in the context of COVID pandemic are briefed below:[3, 4]

- Enable both symptomatic and asymptomatic patients to stay at home and communicate with physicians through virtual channels.
- Break the chain of transmission and to provide rapid access to healthcare services and extra working hands to give physical care.
- Prevent emergency department being overcrowded and to cut down the need of masks, glovesand PPE kits by keeping the patients at home.
- Improve the availability of bed facilities for the needy and to address the patients queries and concerns related to the pandemic on time.
- Perform 'forward triage' prior to the patient's arrival in the primary care clinics.
- Receive home care for patients suffering from other medical ailments, without entering medical facilities, thereby to minimize the risk of contracting the virus.
- Train providers and allied staffs to familiarize safety protocols and policies, use newer tools, revise scheduling processes, and determine triage procedures.
- Maintain records and documents to ease reference and future consultations.

Telemedicine in India and COVID-19

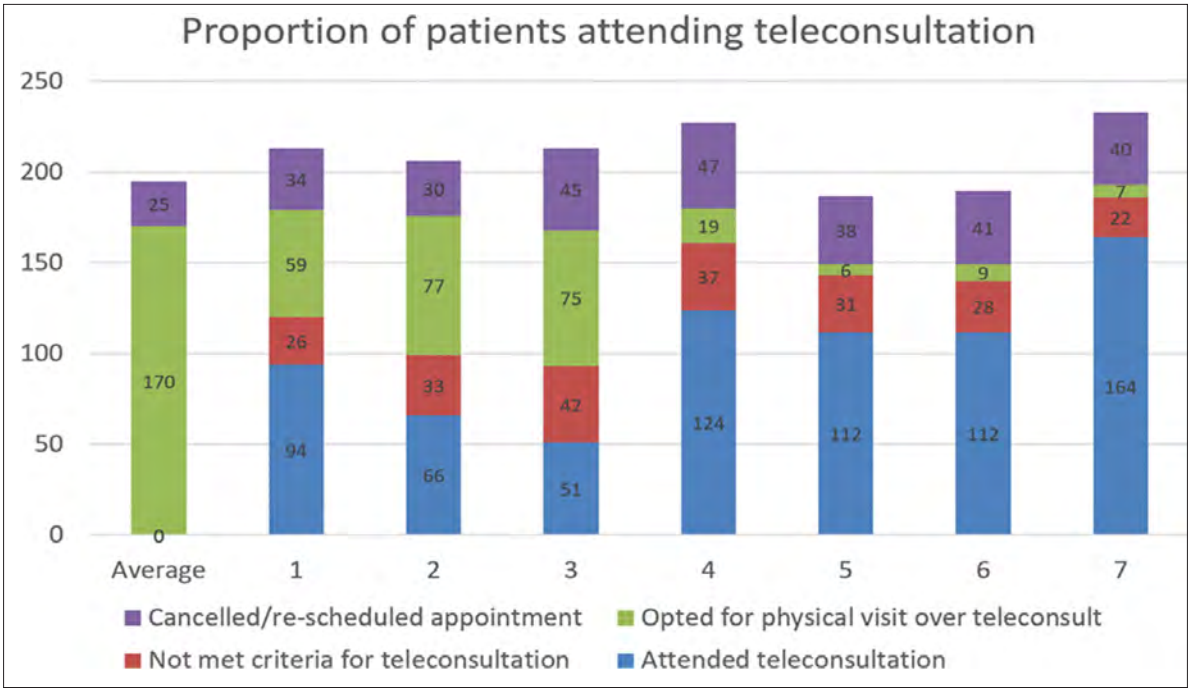
Providing in-person healthcare in India poses a major challenge, owing to the large geographical distances and limited resources/facilities. This is more prominent in rural settings, as there are very limited specialty care facilities and patients need to travel far to access medical services. The Indian government is striving to provide quality care to all needy patients and the implementation of Digital India Mission is helping in wider technology adoption through the use of smartphones, other digital device and mobile apps, providing last mile connectivity and cheaper data plans.[5]

The timely decision by the government to legalize telemedicine helped for the wider adoption of various telemedicine platforms by registered medical practitioners across the country. As a part of employee wellness strategy and facilitate virtual access, many governments, hospitals, e-pharmacies and even corporate have adopted telemedicine post lockdown. The e-consultation platforms like Practo has witnessed nearly 50% increase in the number of doctors joining the digital platform.[6]

A study conducted by Shenoy et al. evaluated the feasibility and patient response in India following

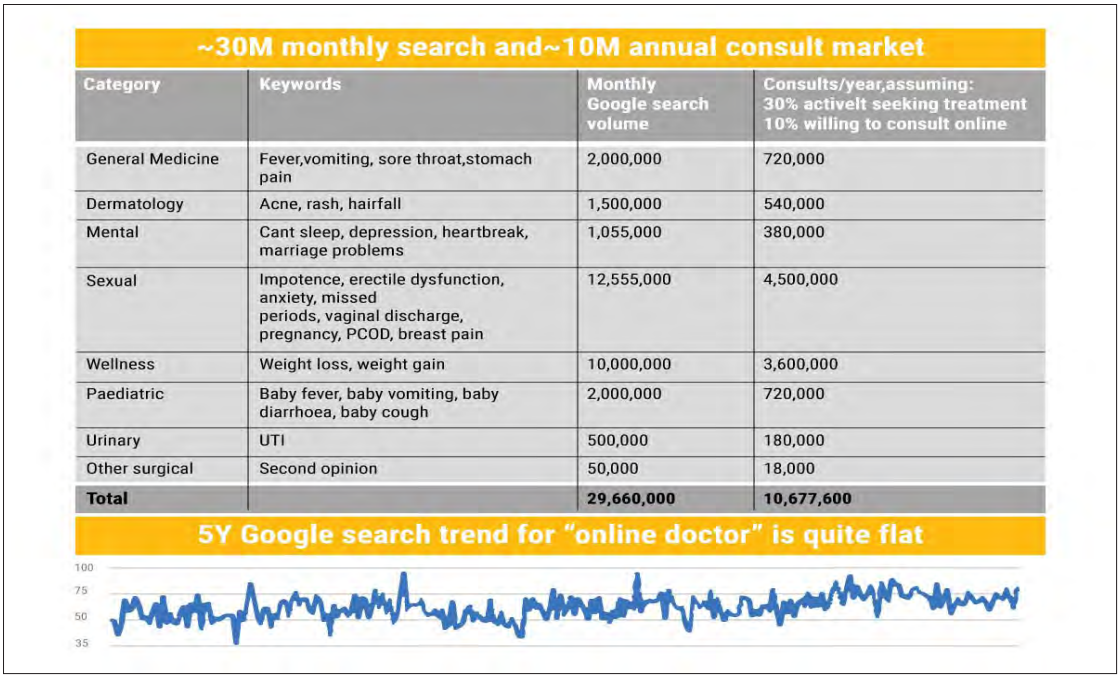
switching to teleconsultation for rheumatology. The adoption of teleconsultation reduced the average footfall to the clinic to 67 (range 29–117). The study has also noted that without the adoption of teleconsultation facilities during the current pandemic situation, nearly three-fourths of the patients would have stopped treatment or resorted to self-medication. The figure 1 depicts the proportion of patients found eligible for and attended teleconsultation as well as proportion who cancelled appointments.[7] In geriatrics, the telemedicine facilities has been adopted considering the increased vulnerability of the population and it has cut down the OPD foot fall of the author's clinic to nearly 90-95%.

Fig. 1: Proportion of patients found eligible for and attended teleconsultation as well as proportion who cancelled appointments.



The overall market size indicate that the teleconsultation is projected to reach 10 million annual consults. The break-up for the different categories for monthly search and annual consult market is provided in figure 2. The study conducted by EY in collaboration with the Indian Pharmaceutical Alliance (IPA), has estimated that the telemedicine market is projected to reach US$5.5 billion by 2025 with teleconsultation and e-pharmacy constituting 90%. Nearly 80% of the surveyed clinicians are using informal means of communication such as audio, video, and texts on various messaging apps for consultation.[8] Swasth alliance, a platform to scale-up tele consults, comprises of at least 92 partners across health-tech companies, diagnostic labs, hospitals, insurance companies, tech companies, and venture capital firms.[9] It offers services to digitize patient data and records, and create online platforms for hospital care and clinician consultations.

Fig. 2: The break-up for the different categories for monthly search and annual consult market



~30M monthly search and~10M annual consult market

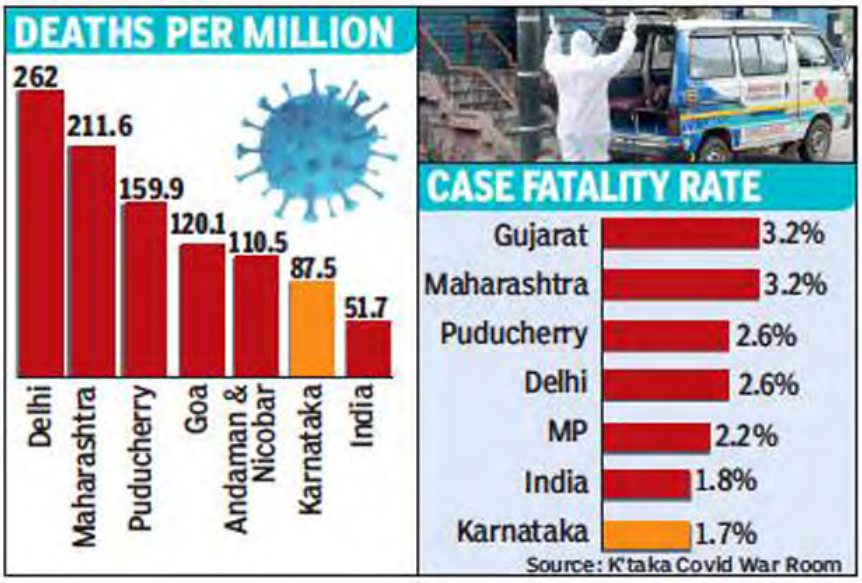
Category	Keywords	Monthly Google search volume	Consults/year,assuming: 30% activelt seeking treatment 10% willing to consult online
General Medicine	Fever,vomiting, sore throat,stomach pain	2,000,000	720,000
Dermatology	Acne, rash, hairfall	1,500,000	540,000
Mental	Cant sleep, depression, heartbreak, marriage problems	1,055,000	380,000
Sexual	Impotence, erectile dysfunction, anxiety, missed periods, vaginal discharge, pregnancy, PCOD, breast pain	12,555,000	4,500,000
Wellness	Weight loss, weight gain	10,000,000	3,600,000
Paediatric	Baby fever, baby vomiting, baby diarrhoea, baby cough	2,000,000	720,000
Urinary	UTI	500,000	180,000
Other surgical	Second opinion	50,000	18,000
Total		**29,660,000**	**10,677,600**

5Y Google search trend for "online doctor" is quite flat

Successful PPP model

In April 2020, the government of Karnataka has come up with an initiative to set up a critical care support team for managing COVID-19.[10] The team has made a network in nearly 30 districts and is conducting e-rounds for twice daily for an hour. The interaction with designated doctors in each district headquarters helps to gather newer evidences on management strategies and interventions. The initiative has handled nearly 1 lakh cases in Karnataka. Such initiatives have helped the state to reduce the case fatality rate drastically (Fig. 3). Moreover, the Union Health Ministry has lauded the initiatives taken by Karnataka with the involvement of multi-sectoral agencies and supported by technology-based solutions.[11]

Fig.3: Case fatality rate and death per million for August 2020



Future of telemedicine

Digital health is the future and embracing technology is inevitable. India's telemedicine market is projected to witness an immense growth and will help to bridge the gap between rural-urban population in terms of medical facilities. It will be the next frontier in the healthcare to create a safe, effective, efficient, in-person and timely health management environment.

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Viral dynamics and reinfection: Do antivirals help in COVID-19?

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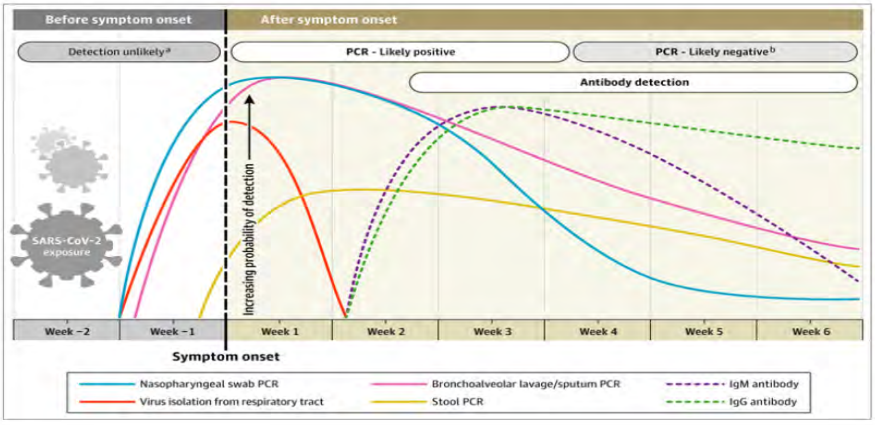
Introduction

Global COVID transmission is increasing at an exponential rate with efficient person-to-person transmission through multiple clusters. Understanding the host immune response, virus dynamics and chances of reinfection is paramount for formulating strategies for infection control, antiviral treatment, and vaccination.

Diagnostic tests relative to symptom onset

A person with SARS CoV2 infection can attain maximum infectivity prior to the onset of symptoms. The peak of replication of virus and its transmission can occur between 2 days before the onset of illness to 3 days after the onset of illness, and it reduces drastically after 5 days or a week. A PCR can detect viral particles up to 90 days, and for the nasopharyngeal swab, the chances of PCR positivity peaks within first week of symptom onset. Virus can be cultured for 10 days to two weeks after the symptom onset. It has been noted that the virus replication lasts longer in bronchoalveolar lavage/ sputum PCR. In stool PCR, the chances of positivity are high for a median of 4 to 11 days. Antibodies are the sensitive and early markers for COVID detection and their levels begin to increase from the second week of symptom onset. IgM antibody becomes positive by 10 days and the levels reduce significantly by 6th week. Whereas, IgG antibody remains positive for about 3 months in majority of the cases (Fig 1).[1]

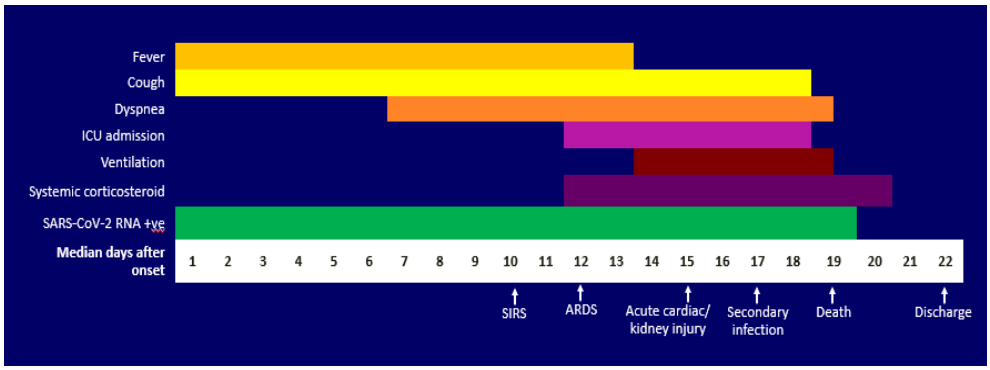
Fig 1: Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset



Clinical course and outcome

The clinical course of SARS CoV2 infection starts with fever and cough, followed by the occurrence of dyspnea in second week. The onset of acute respiratory distress syndrome (ARDS) is generally noted by 10 to 12 days and it can lead to severe illness. The infected person may become extremely ill by second week, and may require ICU admission/ventilation (Fig. 2). [2]

Fig 2: Clinical courses of major symptoms and outcomes



Treatment benefits at different stages of infection

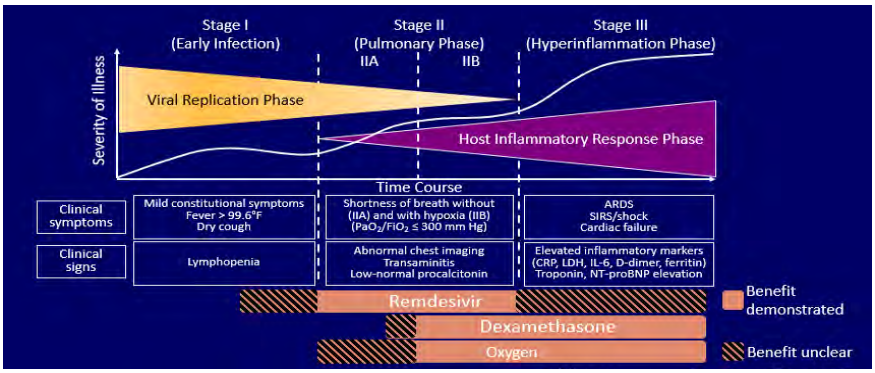
Stage 1, Early infection: The introduction of antiviral during the early phase of infection helps to achieve maximum therapeutic benefit. At present, evidence of clinical experience is available only for IV administration of remdesivir and utmost caution should be taken while patient selection (Fig. 3).[3]

Stage 2, Pulmonary phase: In second stage with the onset of localized inflammation in the lung, the chances for developing viral pneumonia along with cough, fever, and possibly hypoxia, is very high.

Treatment at this stage is mainly supportive measures and anti-viral therapies such as remdesivir. In patients with hypoxia, use of anti-inflammatory therapy such as corticosteroids may be beneficial. (Fig. 3).[3]

Stage 3, Systemic hyperinflammation stage: Stage 3 is the most severe stage of illness with increased risk for extrapulmonary systemic hyperinflammation syndrome. Usage of immunomodulatory agents for systemic inflammation reduction can cause multiorgan dysfunction. Corticosteroids in concert with the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist) may be useful at this stage (Fig. 3).[3]

Fig 3: Benefits of treatment at different stages of infection

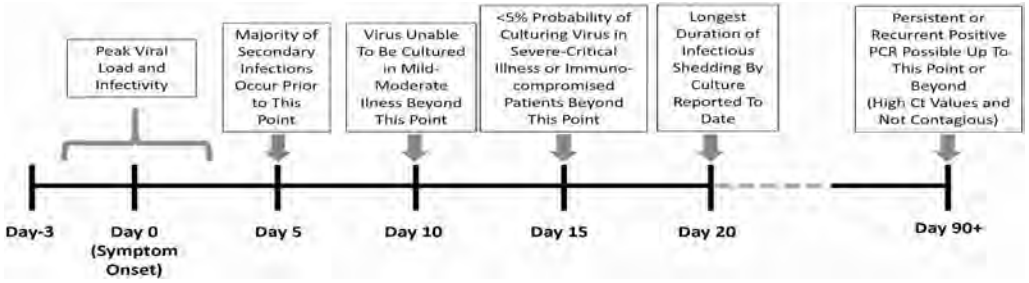


Reinfection with SARS CoV2

In certain cases of recovered and discharged COVID-19 patients, recurrence of clinical symptoms and reinfection may be seen. In majority of the cases, the infection is mild or asymptomatic. Reinfection in the first 90 days may not be considered as true infection, as it can be due to viral shedding, unless the infection is caused due to a different strain. Due to the viral shedding, PCR positivity can be noted in patients even after 90 days (Fig.4).[4] The plausible reasons for reinfection are as follows:

- Weaker immune response after the first infection and immune enhancement
- Genetic defects in the genes encoding Type 1 IFNs contributing to increased severity
- Larger inoculum and presence of more pathogenic strain

Fig 4: Timeline of SARS-CoV-2 infectivity and PCR positivity.



Case studies on reinfection

Case 1: A 33-year-old healthy male, residing in Hong Kong, was diagnosed positive for the first time through SARS-CoV-2 RT-PCR test, conducted using posterior oropharyngeal saliva specimen, on March 26, 2020. He was discharged after hospitalization on April 15, 2020. When the patient was returning to Hong Kong from Spain, via UK, he was tested positive by SARS-CoV-2 RT-PCR using the posterior oropharyngeal saliva specimen taken at the Hong Kong airport on August 15, 2020. After 5 days of hospitalization, serum specimen collected was tested again positive for SARS-CoV-2 IgG using Abbott assay test. Whole genome sequencing performed in both the cases revealed that viral genomes belonged to different clades. The first viral genome belonged to GISAID clade V and the latter one belonged to GISAID clade G.[5]

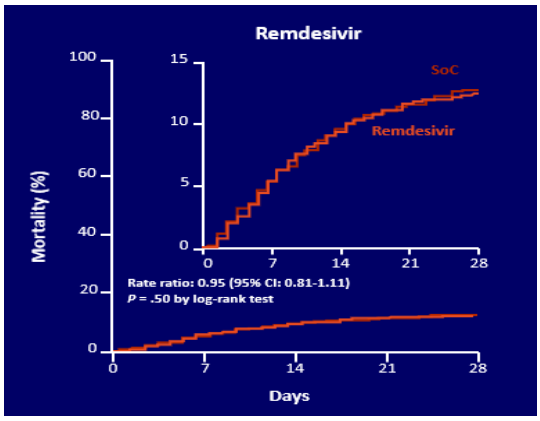
Case 2: A 51-year-old woman residing in Belgium, experiencing mild symptoms like headache, fever, myalgia, cough, chest pain, dyspnoea and anosmia was presented to her general practitioner on 9 March 2020. The patient was administered with a daily dose of oral corticosteroids for asthma. He was tested positive for the first time by a positive SARS-CoV-2 RT-PCR, tested using posterior oropharyngeal saliva specimen with a Ct value of 25.6. The patient underwent self-isolation and had persistent symptoms for nearly five weeks. After 92 days of first infection, the patient was presented with headache, cough, fatigue, and rhinitis and was again tested positive for SARS-CoV-2 (Ct value 32.6). The symptoms lasted for one week and got resolved without hospitalisation. Genome sequencing of both the cases revealed 11 differences with different strains.[6]

Case 3: A 42-year-old healthy male military healthcare worker following a COVID-19 exposure in workplace was presented with cough, subjective fever, and myalgias on 21st March 2020 and was tested positive by SARS-CoV-2 RT-PCR. After 51 days of treatment and monitoring, he recovered to excellent health. Following a new household exposure to COVID-19, on 24th May 2020, the patient was presented with fever, cough, shortness of breath, gastrointestinal symptoms and was tested positive by SARS-CoV-2 RT-PCR. The second infection was more severe than the first. This may be due to contracting infection from a larger inoculum household exposure or more pathogenic strain due to immune enhancement.[7]

Antiviral therapies

WHO Solidarity trial: The trial, recommended by WHO expert groups, was conducted in 30 countries among 45 hospitals. During the study, 11,266 adult patients of ≥18 years old were randomized and allocated to the following groups based on the drug administered: 2750 remdesivir, 954 hydroxychloroquine, 1411 lopinavir, 651 interferon plus lopinavir, 1412 interferon, and 4088 no drug. The primary endpoint of the trial was mortality at 28 days and the secondary endpoint was ventilation and duration of hospitalisation. The study has concluded that the treatment had little or no effect on hospitalized COVID-19 patients (Fig. 5).[8]

Fig 5 : 28-days mortality noted for patients treated with remdesivir or HCQ

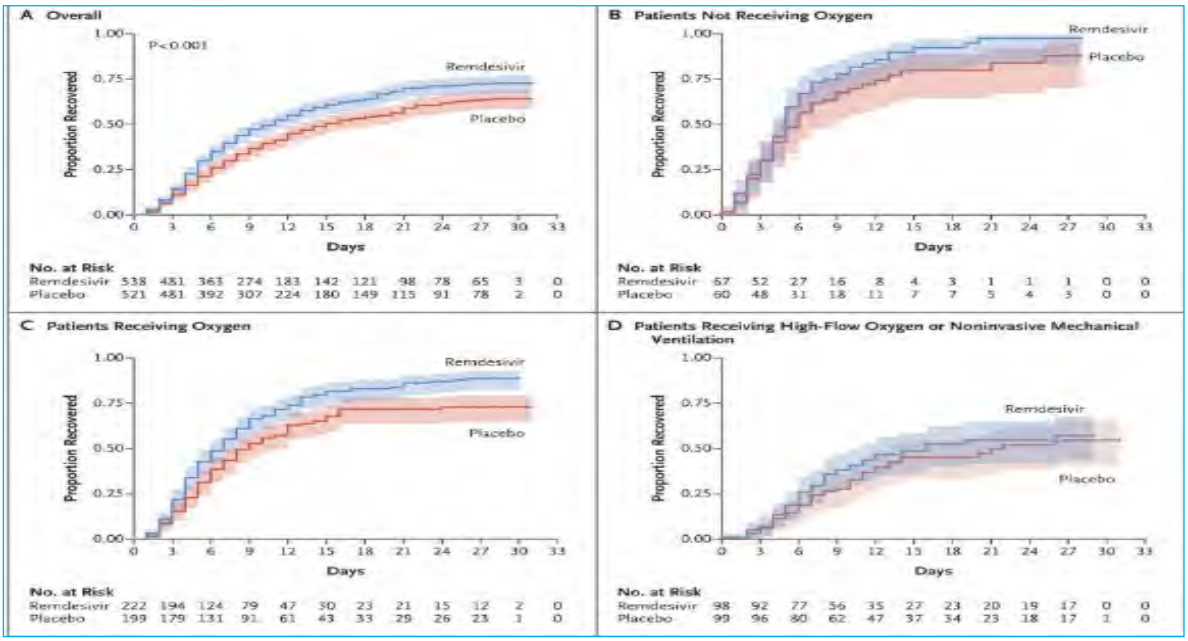


Adaptive COVID-19 Treatment Trial (ACTT-1): The randomized, double blind and placebo-controlled trial of intravenous remdesivir was conducted among 1059 adult hospitalized COVID-19 patients with involvement of lower respiratory infection. Remdesivir 200 mg was given to patient at day 1 and 100 mg at day 2-10 versus placebo. The primary outcome of this trial was recovery time. The study has noted that remdesivir was more effective in patients receiving oxygen and the introduction of remdesivir early, within 10 days was found to be more beneficial (Fig. 6, Table 1).[9]

Table 1: clinical outcome and mortality rate

Outcomes	Remdesivir (n =538)	Placebo (n = 521)	HR (95%CI)	P value
Median recovery time, days	11	15	1.32(1.12-1.55)	< .001
Mortality by 14 days, %	7.1	11.9	0.70(0.47-1.04)	NS

Fig 6: Kaplan–Meier estimates of cumulative recoveries



Remdesivir: 5 days vs. 10 days: A multicentre, randomized, open label phase Ⅲ trial was conducted among SARS-Cov-2 infected hospitalised patients with oxygen saturation of 94% or less. The subjects had radiologic evidence of pneumonia. 200 patients received 200 mg of remdesivir at day 1 and 100 mg at day 2-5. Another group of 100 patients received 200 mg of remdesivir at day 1 and 100 mg at 2-10 days. The corresponding primary and secondary endpoints of this trial were clinical status at day 14 on a 7-point ordinal scale and adverse events that occurred on or after the first dose of remdesivir for up to 30 days after the last dose. Clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group by day 14. The study showed no significant difference between 5 days versus 10 days therapy (Table 2).[10]

Table 2: Clinical outcomes according to the treatment groups

Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)	5-Day Group (N=200)	10-Day Group (N=197)
1: Death	16 (8)	21 (11)
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)
3: Hospitalized, receiving non-invasive ventilation or high-flow oxygen.	9 (4)	10 (5)
4: Hospitalized, requiring low-flow supplemental oxygen.	19 (10)	13 (7)
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	3 (2)

6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	103 (52)
7: Not hospitalized	120 (60)	11

Remdesivir is advisable for patients with COVID-19 pneumonia requiring oxygen. The time to recovery improved by 4 days following remdesivir treatment and faster recovery was noted following the introduction of remdesivir earlier than 10 days. For patients with lower respiratory involvement and increased risk, introduction of remdesivir in early period is beneficial and can shorten the duration of illness. A treatment course of 5 days is recommended, as there is no difference between 5- and 10-days course. However, 10 days therapy is recommended for patients requiring ventilation. Benefit of remdesivir therapy in ventilated and ECMO patients is not yet proven. Adverse effect can be seen in patient with eGFR < 30 ml per minute. Administration of the drug along with HCQ can cause reduction in antiviral activity.

Conclusion

The peak viral and SARS-CoV2 infectivity mainly occur within 2 days before and 3 days after the onset of symptoms and can be detected by RT-PCR test. PCR can remain positive up to 90 days and the virus cannot be cultured beyond 2 weeks in more than 95% of patients. Early initiation of remdesivir, especially in the replication phase of virus (<10 days), can shorten the illness. Reinfection with SARS-CoV2 is very rare and it has not been clinically very relevant, as majority are mild or asymptomatic.

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COVID-19: Home care

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Introduction

Home care is gaining wider interest during the community transmission phase of COVID-19. Like many other viral illnesses, infected individuals and children with mild or no symptoms can be managed at home, which may help in freeing up hospital beds for those with moderate to severe illness as well reduce cost burden on families. However, training the family members or the patient themselves poses a major challenge.

Based on the risk level, the patients requiring home care can be classified as follows:

- **Low risk:** Patients < 50 years with low risk, no comorbidities with no persistence of symptoms after 5 days. These patients can be managed on COVID out patient clinic or by teleconsultations.
- **Moderate risk:** These is the most challanging category, where individuals may have significant disease but they are not experiencing or feeling bad clinical symptoms like low oxygen levels { < 94%}. Other risk factors in these categories are infected individuals with age more than 50 or patients with uncontrolled comorbidities especially diabetes, hypertension and obesity or asthamatics and non verbal or non coperative children.
    - Any patient with persistence of symptoms like high grade fever, weakness or persistent or worsening cough beyond 5 days should be categorised as moderate risk. Above group of patients should be closely watched and mostly require early treatment in hospital settings / seatings.

- **Higher risk:** All patients who develop hypoxia should be considered as high risk population. Any SpO_2 less than equal to 94 percent is defined as hypoxia but more important is to recognise patients before this. It has been observed that once saturation drops below 94 percent patient tend to deteriorate very quickly. There are some indicators which can predict development of hypoxemia like drop in saturation more than 2 from baseline and drop in saturation by 2 after 6 min walk or 1 minutes sit stand test. We should not wait for drop in saturation till or below 94 percent. These patients should ideally be hospitalised. Combination of morbid obesity, uncontrolled diabetes (HbA1c >7.6 percent and persistence of symptoms after 5 days carries high chance of development of pneumonia and hypoxemia and further covid related complications .

Pre-requisites for providing home care

The pre-requisites for home care are as follows:

- Handing over of written management protocols to the patient.
- Emergency care plan.
- Facilities such as calibrated portable finge pulse oximeter, digital thermometer and regular monitoring and follow-up.
- Care giver availability, especially in the case of senior citizen and handicapped patients.
- Nearby healthcare facility and home collection for investigations.
- Isolation facility with separate washroom in case of patients staying with non-infected members.
- Skills to control anxiety and taking care of mental health equally.
- Availability of oxygen cylinder and steroid doses.

Guidelines for clinicians

Appropriate patient selection is paramount, and patients with high risk and low compliance should not be allowed to stay at home. The treating clinician should avoid direct or verbal advice telephonically without directly consulting patient and seeking patient details.

The history collection/ documentation should include age, sex, presence of comorbidities, SpO_2 at rest and after 6 mins walk, drug reconciliation, symptoms of patients such as fever and breathlessness, past serial-wise investigations, and treatment details including steroids. Day of onset of symptoms is most important day considered as day one and not the positive RT PCR day. It is also improtant to ask day of onset of symptoms in index case where one can predict clinical course better as pt consulting you might not be the index case in family.

It is advocated to use an electronic media with video consultation facility to interact with family members. Well-written monitoring plan with treatment plan and warning signs should be given. However, emphasize on efficacy of the drugs/ treatment should be avoided as no drug has been found to be efficacious in treating COVI-19.

RR and SpO_2 criteria considered for classifying COVID-19 stages are briefed in table 1. Important point to be noted that in many patients there may not be drop in spo2 less than 94 percent but significant pneumonia. These patients can be recognised by combining clinical features like persistence of fever

or cough with rise in inflammatory markers and chest imaging. Most appropriate time for getting HRCT is 6th to 10th day or earlier if clinically indicated. Patients who develop hypoxia doesn't need any imaging unless diagnosis is doubtful as management is not going to change.

Table 1: RR and SpO_2 criteria for classifying COVID-19 stages

Clinical Criteria	Mild	Moderate	Severe
SpO_2	>94% in room air, although in some cases significant pneumonia without drop in saturation <95% can be seen.	90-94% in room air	<90% in room air
Respiratory rate (RR)	<24/min	24-30	>30
SpO_2 after 6-minute walk (contraindicated if baseline SpO_2 <95%)	Not significant	Drop of > 2 to 3 (or baseline <94%).	Test is contraindicated

The following are the Do's and Don'ts for clinician involved in home care management.

Do's

- Happy hypoxemia is very common, so clinician should not hesitate to call back patient if anything alarming on monitoring the chart.
- Pulse oximeter measurement to be applied during every session and in case of happy hypoxemia, it can show normal reading without proportional signs of respiratory distress.
- Patients should be regularly monitored for any untoward symptoms.

Don'ts

- Relying on pulse oximeter reading without good wave form
- Commenting on one investigation parameter such as D dimer, IL-6 etc.
- Neglecting fever of any grade after 5 days
- Neglecting drop in SpO2 > 2
- Neglecting breathlessness (In cases of normal SpO2 on day 2)
- Relying only on CT scan reports
- Getting CT scan during initial 5 days unless there is confusion regarding diagnosis

According to NIH COVID-19 treatment guidelines, patients with moderate illness manifest oxygen saturation of oxygen (SpO_2) ≥ 94% on room air at sea level along with evidence of lower respiratory disease during clinical assessment or imaging. Patients with severe illness often present with SpO_2

< 94% on room air at sea level and a respiratory rate of > 30 breaths/min, PaO_2/FiO_2<300 mm Hg, or lung infiltrate >50%.[2] If the SpO_2 drops from 94-95% to 88%, there is a potential risk for ICU admission.[1]

In Indian guidelines unless saturation doesn't drops less than 94 percent disease is not defined as moderate class. There are some subset of patients where saturation is maintained above 94 percent but still there can be significant chest infiltrates as evidenced by study by Saeed et al.

A study by Saeed et al evaluated the correlation between chest CT severity and clinical parameters of 309 patients with COVID pneumonia. The study has noted that there was no oxygen requirement for nearly 50% of the patients with CORAD score 8-17 (with moderate scan findings) and 3.3% of patients with severe scan findings of 18 or more (Table 2).[2]

Table 2: Sum of lobar scores indicating overall severity

Total score (numerical)	Severity (category)
7 or less	Mild
8-17	Moderate
18 or more	Severe

Pathogenesis

Whenever someone is exposed to a significant viral load and gets infected, further course will depend on immunity, viral load, age of the patient, comorbidities (hypertension, uncontrolled diabetes, immunity, heart ailment, pulmonary ailment, dementia etc).

It takes around 3 days after getting the infection (after contact), for a person to become infectious and start spreading the disease. On an average, 6.4 days (2.1-11.1 days) after getting the infection a person can start having symptoms. From treatment point of view disease can be divided into three phases.

1. Symptomatic non pulmonary phase – Cold, cough, fever, malaise, throat pain, myalgia and loose motions are common symptoms . Following these symptoms patient recovers over next 5 to 7 days. Some patients can remain totally asymptomatic throughout the disease process. 85 percent of patients recover from this stage only due to innate immunity. Pathologically in this stage there is predominantly viremia. This is the stage when antiviral therapy like anti viral drugs and antibody therapy can work.

2. Symptomatic Pulmonary phase - Clinically this is marked by respiratory symptoms like fast breathing and drop in saturation below or equal to 94%. Two pathological processes can lead to this phase, pulmonary thrombosis and immune dysregulation. There is less viral replication after 10 days but over reaction to viral debris in form of immune dysregulation. Immune dysregulation can manifest as cytokine storm, macrophage activation syndrome. This phase

in few of patients manifest with persistence of fever or reappearance of high grade fever or raising inflammatory markers.

Pulmonary phase can be divided in two parts – early and late. Early is "L" type where elastase is low and invasive ventilation should be avoided as much as possible. At this stage anti inflammatory and anti thrombotic therapy plays a major role. If disease progresses this can lead to late pulmonary phase "H" type, with high elastase and behaves like classical ARDS (Fig 1).[3]

In the initial stages of 5-7 days, most of the patients show non-respiratory symptoms. The 8-12 days of infection is called early pulmonary phase, and most of the patients may require hospital admission. Other classic features of this stage are SpO_2 > 94% and chest infiltrate manifestation in HRCT (not on X-ray). Intervention at this stage can be beneficial to prevent morbidity.

Fig 1: Stages of COVID-19

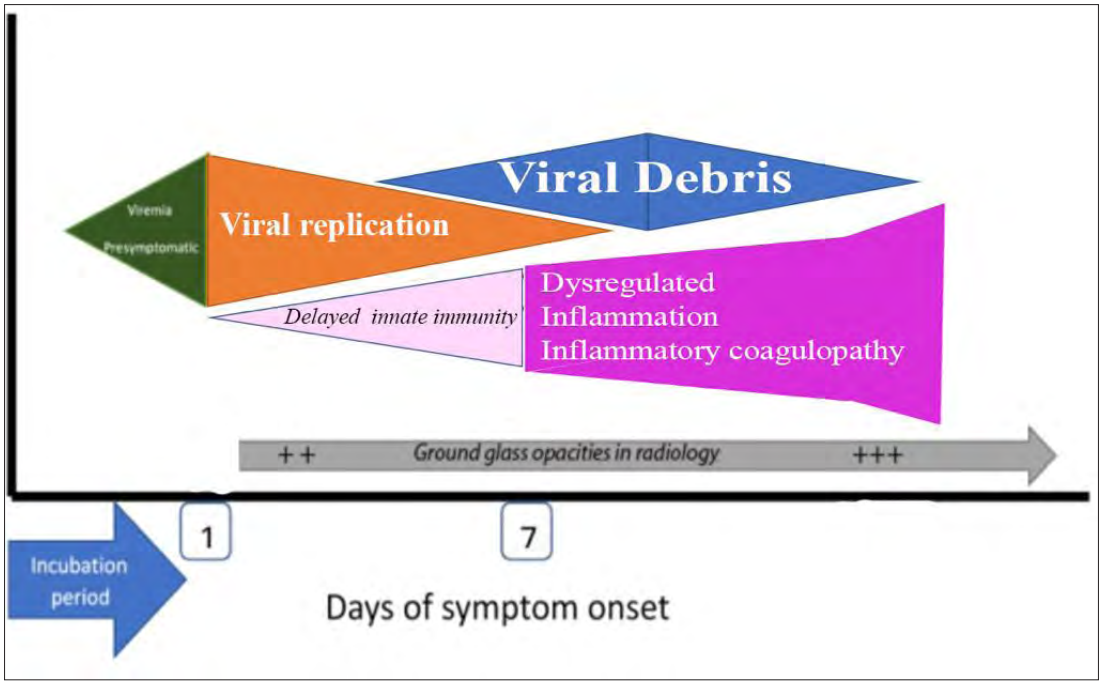
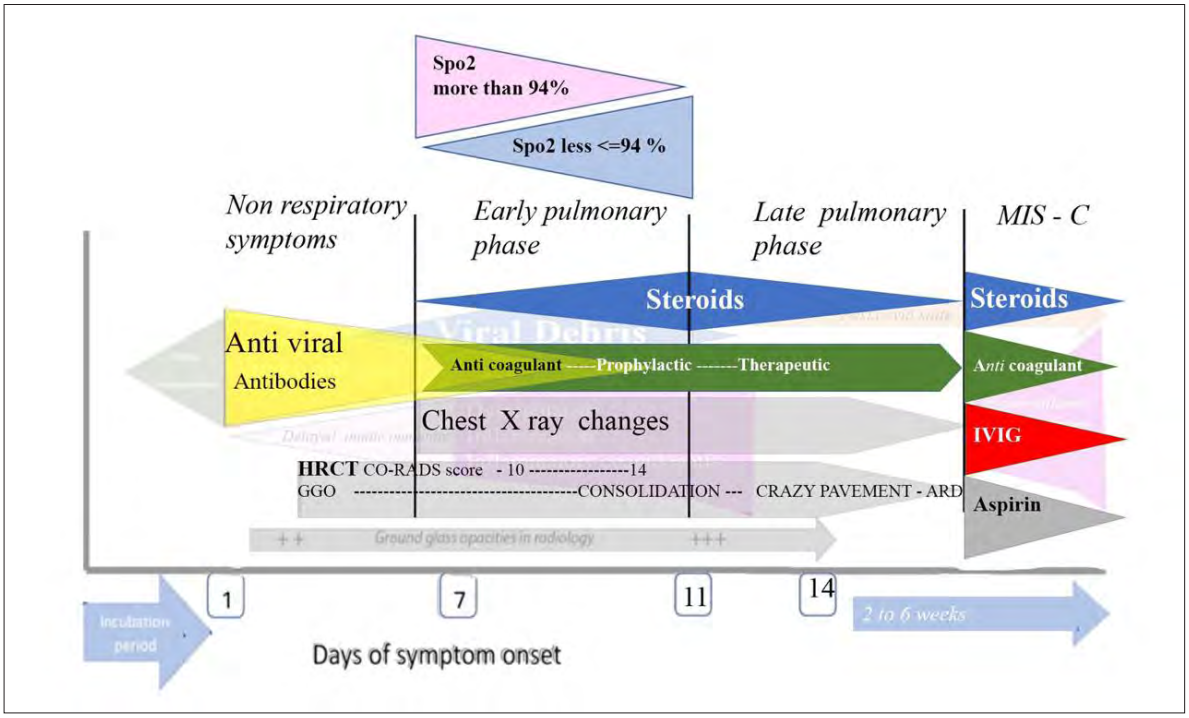


Fig. 2: Pathogenesis Chart



Moderate cases definition should be modified by incorporating imaging in high-risk patients, as when oxygenation reaches <94%, the patient's condition may deteriorate faster.

COVID-19 spectrum: Treatments options

The suggested treatment options based on COVID spectrum and severity are listed below:

- **Acute COVID, asymptomatic:** This group does not require any treatment.
- **Acute COVID patients with upper respiratory tract infection:** Favipiravir may be advisable in high age group with co-morbidities but efficacy is doubtful.
- **Acute COVID patients with pneumonia (LRTI):** Remdesivir, enoxaparin and steroids may be advisable.
- **High risk patients with evidence of significant inflammation or pneumonia should be admitted early and may require to treat with anti-viral drugs like** Remdesivir and monoclonal antibodies.

Risk stratification

The factors to be considered for the classification of COVID patients as high risk include age >50, co-morbidities such as obesity and diabetes, family history of death due to COVID, male gender and A blood group. The symptoms to be considered for high-risk classification include persistent fever for >5 days, high-grade fever >102°F beyond 2 days, chills, rigor, breathlessness, and biphasic

fever. Clinical investigations such as elevated CRP, significant chest infiltration in radiology (CORAD severety score more than 10 /25) and presence of hypoxemia (drop from the baseline < 94-95%) are the other classic features to be considered for high-risk stratification.

Case studies on COVID-19

Case 1: A 72-year-old male with a history of fever, cold and cough for the past 12 days presented with recurrence of fever 101-102°F in the last two days. The patient was non-diabetic, normotensive, overweight and had certain cardiac abnormalities. He did not show an increase in respiratory rate or breathlessness and SpO2 was 96% at room air. Patient was at high risk, but denied to get hospitalized. He was initiated with dexamethasone 6 mg once a day and subcutaneous enoxaparin (40 mg) once a day and there was no requirement of oxygen. Results of clinical and lab investigations are depicted in table 3.

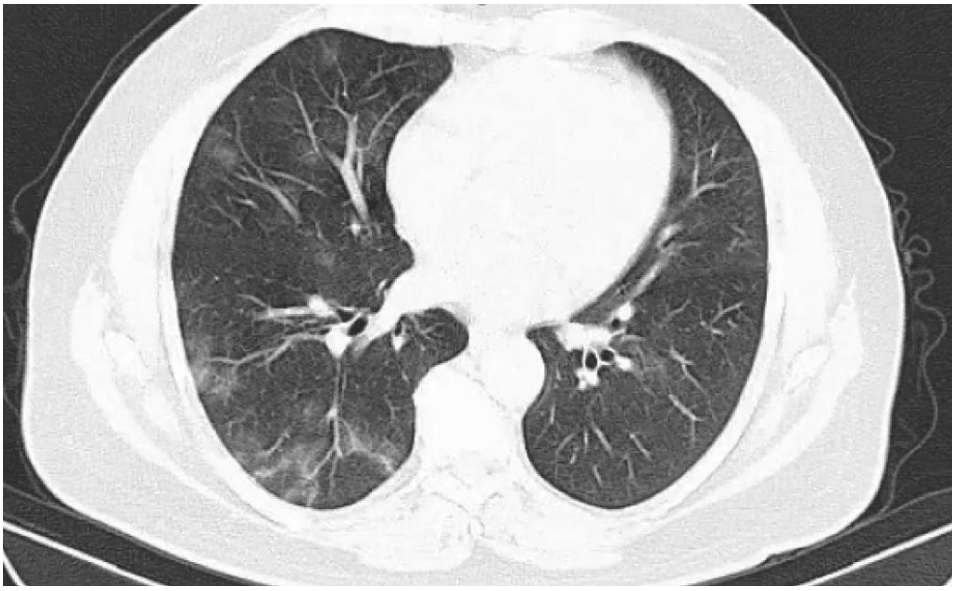
Table 3: Findings of clinical and lab investigations

Laboratory test	Normal	Patient reports	Significant
NLR (Neutrophil-Lymphocyte ratio)	<3.5	3.99	>5.5 (Pre-steroids)
CRP (mg/L)	<40	25(<5)	>100 and rising
Ferritin(ng/ml)	<500	556	>700 and rising
D-dimer (ng/ml)	<0.5	0.73	>1.0
LDH (U/L)	<300		>400 and rising

Remdesivir / Favipiravir was not given, as these drugs do not have any role post 12 days, except in critical patients. The patient was instructed to get admitted if any of the following symptoms were noted: chest pain, breathlessness, heaviness in chest, mental confusion, decreased urine output, poor oral intake, persistent vomiting, bluish discoloration of nails and lips, drop in SpO_2 from baseline (<94% or by 4 after 6 min walk), high grade fever (>102 °F), and persistence of symptoms after 5 days of onset. Investigations were done every third day including CRP, D-dimer, ferritin, KFT, LFT, uric acid, HbA1C, and TFT. Steroids tapered over 2 weeks and anticoagulants were given for 4 weeks.

Case 2: A 71-year-old male, doctor by profession, with obesity and diabetes was diagnosed with COVID and he preferred home care. From day 1 to 9, the patient received favipiravir. The remarkable clinical findings were SpO_2 96-98%, CRP<10 mg/L, and D dimer <0.5 mg/ml. On 9th day, the patient complained of recurrence of fever and he was suggested to start Remdesivir and repeat CRP though there was no drop in oxygenation. He was not hypoxic and only persistence of fever was noted. At this stage he was initiated with steroids. Test results of hematologic examination and CT revealed elevation of CRP from 8 to 21 mg/L and CT severity score of 18 respectively.

Fig. 3: CT scan

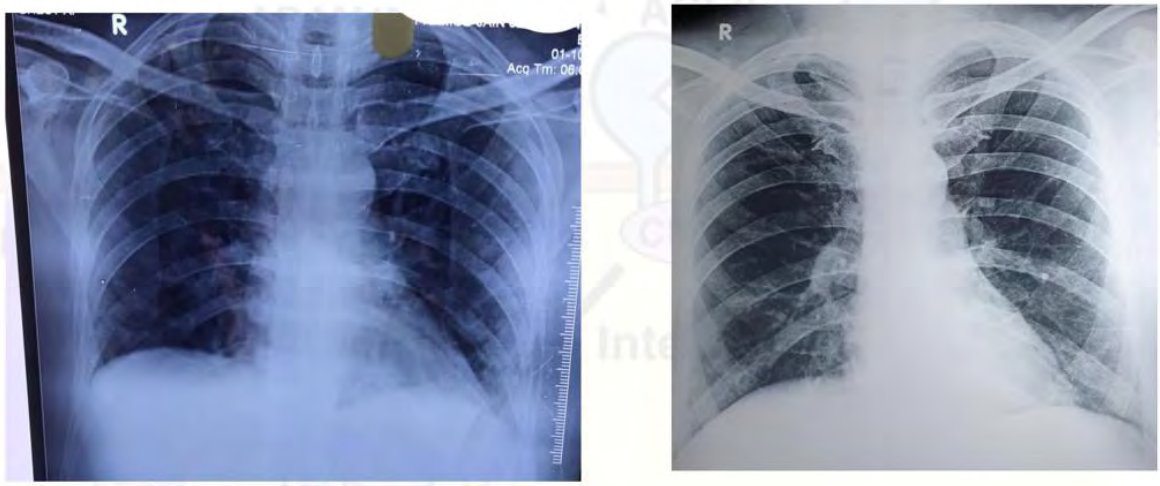


Learning points

- Patients in home care should be strictly followed for features like recurrence of high fever.
- Subjects with morbid obesity or poorly controlled diabetes should not be managed at home.
- Waiting for drop in saturation to less than 94 percent is late sign.

Case 3: A 53-year-old male, doctor by profession presented with low-grade fever. Clinical investigation on day 5 revealed normal CRP and normal D dimer. CT scan on day 7 showed 8/25 score. The patient was initiated with Favipiravir and Enoxaparin. On 9th day, the patient showed recurrence of fever (99.8°F), SpO2 95%, CRP level 7.3 mg/L and D dimer 281 ng/L. The patient was admitted and was started with remdesivir. Next 10 days in hospital were eventful with high oxygen requirement. Even after day 40, the patient had chest infiltration and persistence of cough (Fig. 4).

Fig 4: Comparison of chest X-ray between day 10 and 40



Learning points

- Drugs like Ivermectin, Favipiravir, Doxycycline, Azithromycin, Zn, Vitamin C, Methylene Blue, Steam, Betadine gargles do not have much role.
- Any clinical sign is a red alert, whether it is high fever, elevated CRP, persistence of fever and cough or any other inflammatory signs.
- Drugs like Favipiravir, Ivermectin, Doxycycline, Azithromycin, HCQ are comparable to placebos and doesn't have major role in actual management .
- Radiology if used appropriately plays an important role.

Case study 4: A 54-year- old male with no obesity and diabetes, who lost his brother on 4th day due to acute MI secondary to COVID-19, presented to the clinic. Patient had persistence of fever>101°F and was tested COVID positive on day 4th. He was admitted and was initiated with remdesivir for 5 days. From day 8-14, the patient remained asymptomatic. On day 15th, the fever recurred, without elevation in inflammatory markers. Within 12 hours, his oxygen saturation dipped from 98% to 95%. Steroid were started from 16th to 21st day. His oxygen requirement increased to 10 litres oxygen. The patient recovered following treatment.

Learning points

- Initiation of drugs like remdesivir, even at an early stage of disease, does not confer protection against progression to inflammatory phase. May require to give this drug for 10 days
- Male gender, family history of significant pneumonia secondary to COVID-19 and A-positive blood group are high-risk factors.

Conclusion

- Regular and close monitoring is essential for high-risk COVID-19 patients.
- When ever there is drop in oxygenation patient should be admitted with steroid cover (immediately one dose of steroid should be given with 2 hours).
- In high risk situations (persistence of fever after 5 days, comorbidities)
- It is ideal to perform imaging between 6^{th} to 12^{th} day after the infection onset if there is confusion about management plan
- Once hypoxia is set then again there is no need of HRCT as management plan is not going to change.
- Late immune dysregulation (14 days onwards) is again not uncommon even after early remdesivir treatment , there patients should be watched for pneumonia till 21 days post symptoms .
- For managing high risk patients at home Oxygen and Methylprednisolone should be ready as contingency emergency plan.
- Pulse oximeter reading should be monitored carefully after 6 mins exercise walk test.
- Clinician should not give opinion on anonymous calls and reports.
- Morbid obese patient with uncontrolled diabetes should not be managed at home.

COVID MONITORING AT HOME

NAME:	ANY ALLERGY
RT PCR +ON DATE:	ANY SURGERY
MEDICAL PROBLEMS:	WEIGHT: HEIGHT:
TAKING MEDICINES:	MALE/FEMALE:

DAY OF SYMPTOMS																			
DATE:																			
TIME: 8 AM																			
TEMPERATURE:																			
SPO2 AFTER WALK FOR 6 MINUTES:																			
PULSE RATE:																			
TIME: 3 PM																			
TEMPERATURE:																			
SPO2 AFTER WALK FOR 6 MINUTES:																			
PULSE RATE:																			
TIME: 9 PM																			
TEMPERATURE:																			
SPO2 AFTER WALK FOR 6 MINUTES:																			
PULSE RATE:																			

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Severe Acute Respiratory Syndrome Corona Virus 2 (SARS – CoV-2) Pediatric Aspects

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INTRODUCTION:

Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Coronavirus causes a wide variety of diseases in various animal species. It is known to cause innocuous respiratory infections and occasional viral diarrhea in humans. Pandemic caused by SARS-CoV-2 (a beta corona virus) is a third spill over in two decades of an animal corona virus to humans- SARS – CoV, MERS CoV and SARS – CoV-2.

EPIDEMIOLOGY:

SARS-Cov2 virus is closely related to to BatCoV RaTG13, a bat coronavirus that was previously detected in Rhinolophus affinis from Yunnan Province, with 96.2% overall genome sequence identity. SARS CoV 2 is primarily transmitted between people through respiratory droplets and contact routes. Droplet transmission occurs when a person is in close contact (within 1 m) with someone who has respiratory symptoms(1). Airborne transmission refers to the presence of microbes within droplet nuclei (<5μm in diameter), can remain in the air for long periods of time and be transmitted to others over distances greater than 1 m.There is also gastrointestinal tract (intestine) tropism of SARS coronavirus (SARS-CoV) which was verified by the viral detection in biopsy specimens and stool. Though droplet and aerosol transmission plays a major role in the transmission of SARS-

CoV-2, fomite transmission is possible since it can remain on surfaces upto days (depending on the inoculum shed).

PATHOPHYSIOLOGY OF COVID-19

Coronaviruses possess the largest genomes among all known RNA viruses. In the case of SARS-CoV2, the spike glycoprotein (S protein) on the virion surface mediates receptor recognition and membrane fusion (2,3). It utilizes Angiotensin converting enzyme 2(ACE 2) receptor for cell entry. ACE2 is a type I membrane protein expressed in lungs, heart, kidneys, and intestine.

Stage I. Viral entry and replication: In the first stage of the disease, the virus attaches itself and multiplies in the mucosa, which is the incubation period and the infected person usually remains asymptomatic. This period lasts from 2 to 7 days with a mean of 4-5 days. The symptoms then start and consists of fever (which may be high or even completely absent), constitutional symptoms like headache, body ache, dry cough, throat pain, anosmia, ageusia and diarrhea. However, some individuals and especially children can remain almost totally asymptomatic all through the illness.2,3

Stage II.- Pulmonary phase: In the second stage of pulmonary disease, viral multiplication occurs in the lungs due to the high expression of ACE2 receptors. The primary involvement is the ACE2 receptor expressing alveolar type II cells, generally at the periphery of the lung. As the virus replicates within these type II cells, the affected cells undergo apoptosis and release a large number of viral particles to infect the neighbouring cells. With progressive loss of type II alveolar cells, surfactant production is affected leading to micro-atelectasis. This causes the streaky infiltrates on chest imaging (by radiography or CT) and finally a ground glass appearance. The alveolar type II cells are also the precursors of the type 1 cells that maintain the integrity of the alveolar lining and permit gaseous exchange. Hence, when the alveolar type I cells get involved there is impaired gaseous exchange leading to hypoxia. The pathological result is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. Aberrant healing of alveolar lining may lead to scarring and fibrosis that may present as ARDS. A combination of hypovolemia, hyperinflammation and direct cytopathic effect of virus has been implicated in the pathogenesis. 2,3

Stage III. Hyperimmune response phase: This stage is not seen in all patients. A majority of children seem to recover after stage II or even directly after stage 1. A minority of COVID-19 patients will enter into the third and most severe stage of illness, which manifests as systemic hyper inflammation syndrome. A form similar to hemophagocytic lymphohistiocytosis (sHLH) may occur in patients in this advanced stage of disease. In this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable. Critically ill COVID-19 patients are prone to develop frequent thrombotic manifestations like pulmonary embolisms (20–30% of cases), deep vein thrombosis(DVT), as well as arterial thrombosis like ischemic strokes. 2,3

CLINICAL FEATURES:

Pediatric coronavirus disease – 19 (COVID-19) is relatively mild when compared to adults, and children are reported to have a better prognosis.[3,4]

1. *Asymptomatic infection:* Without any clinical symptoms and signs and the chest imaging is normal, while the 2019-nCoV nucleic acid test is positive (4%).

2. *Mild (uncomplicated upper respiratory infection):* Symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing.

3. *Moderate (Pneumonia with no signs of severe disease):* With pneumonia, frequent fever and cough, mostly dry cough, followed by productive cough, some may have wheezing, but no obvious hypoxemia such as shortness of breath. Some cases may have no clinical signs and symptoms, but chest CT shows lung lesions, which are subclinical (39%).

4. *Severe (severe pneumonia):* Early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease usually progresses around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations (5%).

5. *Critical:* Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life threatening.

DIAGNOSIS:

The most commonly used and reliable test for diagnosis of COVID-19 has been the RT-PCR test as per current guidelines. Other laboratory tests and imaging modalities offer supportive evidence. Viral cultures and Genome sequencing are usually performed only for research purposes.

Molecular tests (Nucleic acid amplification tests/ NAAT[5]:

Nucleic acid amplification tests done on respiratory samples are currently the gold standard for diagnosing COVID-19. WHO recommends first line screening with the E gene assay followed by a confirmatory assay using the RdRp (RNA dependant RNA polymerase) gene .The molecular test is performed on the upper respiratory or lower respiratory samples. Viral RNA in the nasopharyngeal swab as measured by the cycle threshold (Ct) becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset. In a study of 205 patients with confirmed COVID-19 infection, RT-PCR positivity was highest in BAL specimens (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swab (32%) , but the specificity is 100%.A newer molecular diagnostic method called Xpert Xpress SARS-CoV-2 provides test results based on the detection of two gene targets(N2 and E gene). However this test does not require separate DNA extraction and hence can deliver results within 2 hours after submission of the sample. It also does not need technical expertise

and can be run as an individual test and samples need not be batched. It is particularly useful when rapid results are needed.

Rapid Antigen Detection Test for COVID-19:

The only antigen assay available in India is Standard Q COVID-19 Ag detection kit.(5) It is a rapid chromatographic immunoassay for qualitative detection of specific antigens to SARS-CoV-2.The test is performed on the nasopharyngeal swabs and the results are available in 15-30 minutes. It has a very high specificity from 99.3 to 100% and but the sensitivity of the test ranges from 50.6% to 84%, depending upon the viral load of the patient. Therefore, suspected individuals who test negative for COVID-19 by rapid antigen test should be definitely tested sequentially by RT-PCR to rule out infection, whereas a positive test should be considered as a true positive and does not need reconfirmation by RT-PCR test.

Hematological, biochemical and immune parameters:

The changes in the WBC count (neutrophilia or lymphopenia) is not very much pronounced in children as in adults and inflammatory markers like CRP, PCT and LDH can be used for monitoring the disease progression along with the clinical status of the child.

Radiology: According to the American College of Radiology (ACR) appropriate criteria, imaging is not indicated in a well appearing immunocompetent child ≥ 3 months of age who does not require hospitalization. However, due to limited sensitivity and specificity, a negative CXR does not exclude pulmonary involvement in patients with laboratory confirmed COVID-19 nor does it indicate absence of COVID-19 infection in cases of suspected COVID-19 infection not yet confirmed by RT-PCR.

Although the chest CT findings of COVID-19 in the pediatric population are not pathognomonic, a bilateral peripheral sub pleural lower lobe predominant pattern of ground-glass opacities is suggestive of the diagnosis in the appropriate clinical setting. Thus the ACR currently recommends against using CT as a first line screening test to diagnose COVID-19 and states that chest CT should be reserved for symptomatic hospitalized patients with specific clinical indications. 6

MANAGEMENTOF COVID-19:

Implement IPC measures for Children with suspected or confirmed COVID-19 (7)

Instructions for patients – Surgical face mask; cough etiquette.

Apply contact and droplet precautions:

Air borne precautions: While performing aerosol-generating procedures

Mild and moderate COVID-19:

Children with mild and moderate COVID-19 may not require emergent interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases to contain virus transmission. There is no indication for antibiotic therapy or prophylaxis for patients with mild COVID-19. For children with moderate COVID-19 also, antibiotics should not be prescribed routinely unless there clinical suspicion of a bacterial infection. They can be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration.

Management of severe COVID-19: severe pneumonia:

Children with signs of severe pneumonia should receive immediate airway management and oxygen therapy during resuscitation to target SpO2 ≥ 94%. Once patient is stable, the target is > 90% SpO2. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated. Use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment should be done as soon as possible. Antimicrobial therapy should be assessed daily for de-escalation. In children with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bi level positive airway pressure (BiPAP) may be used. Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial.[7]

Management of critical COVID-19-septic shock:

Standard care includes early recognition and the following treatments within 1 hour of recognition: antimicrobial therapy, and initiation of fluid bolus and vasopressors for hypotension.In children, epinephrine is considered the first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine.

Role of Medications:

Remdesivir: Adoptive COVID-19 Treatment Trial (ACTT Trial) 8-based on the results of this study, remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection. All-cause mortality was 11.4% with remdesivir and 15.2% with placebo(8). However the results from a systematic review and network meta-analysis that pooled data from four randomised trials with 7333 participants hospitalised for covid-19. Of note, none of the included RCTs enrolled children or adolescents under the age of 19 years. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain. When moving from evidence to the conditional recommendation against the use of remdesivir for patients with COVID-19 - no effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. Remdesivir may be used for pregnant women and children only as compassionate drug use. Dosing guidelines:

<40 kg: 5 mg/kg IV loading dose on day 1; then 2.5 mg/kg IV OD.

>40 kg: 200 mg IV loading dose on day 1; then 100 mg IV OD.

Steroids: Studies have shown that there is evidence of a 28 day mortality reduction of 8.7% in the critically ill and 6.7% reduction in patients with severe COVID-19 who were not critically ill when systemic corticosteroids were used. The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Similarly, Recovery trial(9) recommends that steroids may be beneficial to those who are on mechanical ventilation but the use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis, and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only).

Other drugs: None of the studies support the use of Chloroquine or hydroxychloroquine with or without azithromycin, Lopinavir/ritonavir, Ivermectin.

PEDIATRIC INFLAMMATORY MULTISYSTEMIC SYNDROME- TEMPORALLY ASSOCIATED WITH COVID-19

It is defined as a syndrome in which children present with persistent fever, inflammation, and evidence of single or multi-organ dysfunction, with exclusion of any other microbial cause, with or without PCR evidence of SARS-CoV-2(10). Even though children with PIMS-TS shares many clinical features with complete and incomplete kawasaki disease, it usually occurs in older children and adolescents who were previously healthy. Common clinical features of MIS-C include fever, mucocutaneous findings (rash, conjunctivitis, edema of the hands/feet, red/cracked lips, and strawberry tongue), myocardial dysfunction, cardiac conduction abnormalities, shock, gastrointestinal symptoms, and lymphadenopathy. Neurological involvement is also frequently reported and manifests as head ache, altered mental status, cranial nerve palsies or meningism CBC with manual differential, CRP, Urea, creatinine and electrolytes, LFT and testing for SARS-CoV-2 by PCR and serology constitutes the 1st line of investigations. If children have elevated ESR and/or CRP and at least 1 other suggestive laboratory feature: lymphopenia, neutrophilia, thrombocytopenia, hyponatremia, or hypoalbuminemia (11), then step 2 investigations can be planned. ECG and echocardiogram, troponin T and N-terminal-proBNP, may help identify children with cardiac sequelae. A stepwise approach to immune modulatory treatment in PIMS-TS is recommended, with intravenous immunoglobulin (IVIG) and/or glucocorticoids considered first line agents.If they are resistant to IVIG and glucocorticoids, other immunomodulators like anakinra or tocilizumab or TNF-á blockade with infliximab can be tried.

VACCINES:

Antiviral vaccines can be classified into two broad categories.

i) **Gene-based vaccines** deliver gene sequences that encode protein antigens that are produced by host cells. These include live-virus vaccines, recombinant vaccine vectors, or nucleic acid vaccines.

ii) **Protein-based vaccines** include whole-inactivated virus, individual viral proteins or sub domains, or viral proteins assembled as particles.

There are currently more than 143 candidate vaccines undergoing preclinical development and 33 vaccines in clinical evaluation, according to WHO (12). More than a dozen candidate vaccines are in phase 1 to phase 3 trial. Challenges to developing an effective vaccine consist of identifying the appropriate antigen, whether S protein or receptor binding domain proteins provoke more protective antibodies, prior exposure to adenovirus serotype 5 [which impairs immunogenicity in the viral vector vaccine], need for adjuvant, need of large scale production and regulation (eg, ensuring safety and effectiveness), and legal barriers (eg, technology transfer and licensure agreements).

FUTURE:

The genetic epidemiologic investigations identified an emerging D614G mutation affecting the spike glycoprotein of SARS-CoV-2 strains from Southern Europe; this variant has since spread rapidly and has become the most prevalent genotype worldwide (13). Patients infected with D614G-associated SARS-CoV-2 are more likely to have higher viral loads in the upper respiratory tract than patients infected with virus strains without the mutation, but disease severity is not affected. These findings raise critical questions regarding the future evolutionary trajectories of the SARS-CoV-2 G614 variant. Will these selective pressures drive antigenic variation, promote virus stability and transmissibility, alter virus virulence and pathogenesis, or drive SARS-CoV-2 to extinction or into alternative hosts as reservoirs?

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Everything about COVID-19 vaccines from trials to tray

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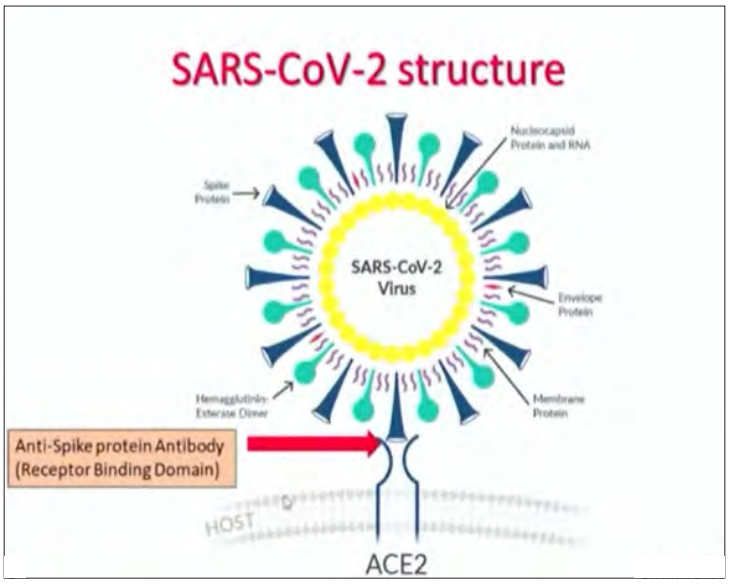
Introduction

Most of the countries are planning to roll out the vaccine in next few months. However, the WHO has cautioned that vaccine may not serve as a magic bullet for mitigating the pandemic. The main feature of SARS-Cov2 virus pathogenesis is the entry to the host cell via surface activation of ACE2 by protein spikes of the virus (Fig 1). Severe form of the disease is linked to substantial morbidity and mortality in elderly and people with comorbidities.1 Most of the vaccines target the ACE2 receptor binding domain of spike protein binding to the ACE2. Cross-reaction of the SARS-CoV RBD-specific antibodies with SARS-CoV-2 RBD protein, and SARS-CoV RBD-induced antisera leading to the cross-neutralize SARS-CoV-2, there by suggesting the potential of RBD-based vaccines for preventing the infection.

Fig. 1: Structure of SARS-CoV2 virus



COVID-19 vaccines

The vaccines under development against SARS-CoV-2 include whole virus vaccines, nucleic acids vaccines, viral vector vaccines and protein-based vaccines. COVID-19 vaccines include both whole cell-inactivated and live attenuated vaccines. Protein-based subunit vaccines are considered as the safest formats, but immune responses elicited by these kind of vaccines are heavily dependent on the adjuvant used. Scientists at the University of Oxford are in the process of manufacturing chimpanzee adenoviral vector vaccine for COVID-19. Some of the repurposed vaccines that are purported to provide non-specific protection include BCG, rBCG, MMR, Measles, Rotavirus vaccine, OPV and Sepsivac.

T cell response to COVID-19

Emerging literature evidence suggests that majority of the COVID-19 patients develop a strong and broad T cell response, both CD4 and CD8-mediated. Studies in recovered patients have shown that 100% have specific CD4+ response and 70% have specific CD8+ response. The reaction of CD4+ is directed towards spike protein, M, N, and other proteins such as nsp3, nsp4, ORF3a and ORF8, whereas, CD8+ response is aimed at spike, M proteins and 8 more ORF targets. Nearly 40-60% of unexposed individuals also have reactive CD4+ T cell recognition due to their exposure to other common cold viruses, which have similar structure as that of human corona virus.[2]

Phases of vaccine trials

- **Preclinical:** In this phase, animal-model based tests are conducted to evaluate the potential of the vaccine.
- **Phase 1:** Trials are done on small numbers of patient population to detect the safety of the vaccine.
- **Phase 2:** Smaller cohorts of all ages are evaluated for proof-of-concept, dose, determination of immunogenicity and safety and doses of vaccine.
- **Phase 3:** A larger number of patient population of all ages is studied for extended safety, immunogenicity and efficacy if applicable.
- **Phase 4:** This phase is intended to evaluate post-marketing surveillance, safety, effectiveness, and impact of vaccine in larger populations.

Chance of success of a vaccine from preclinical phase to final phase is 7% and for phase 2 to final phase of trial is 20%.

Status of global vaccines for COVID-19

- **Preclinical:** Around 179 vaccine candidates are still in preclinical phase and could not make it yet to human trials.
- **Phase 1**: 36 vaccines are in phase 1 for testing the dosage and safety.
- **Phase 2:** 14 vaccines are in phase 2 trials for expanded safety trials.
- **Phase 3:** 6 vaccines are in large-scale efficacy trials.
- **Approved for use/limited use and licensed:** 3 vaccines namely Sputnik V and EpiVacCorona from Russia, Cansino from China have been licensed and approved.

International collaboration

Some of the major international collaborations formed for the development of the COVID vaccines are listed below:

- Russian Investment DirectFunding (RDIF)
- Operation Warp speed (OPW) and Accelerated COVID-19 Therapeutics Interventions and Vaccines (ACTIV) by USA are tied up with 18 companies.
- Moderna, Oxford, Pfizer vaccines have been chosen for phase 3 trials. Vaccines with at least 50% efficacy will be licensed by US FDA, as per June 2020 guidance.
- WHO presented Accelerated COVID-19 Tools (ACT) to provide innovative and equitable access to diagnostics, treatments and vaccines.
- The vaccine pillar of the ACT Accelerator-known as the COVAX Pillar-is designed to accelerate the development of COVID-19 vaccines.

COVAX is spearheaded by Coalition for Epidemic Preparedness Innovations (CEPI), GAVI the vaccine alliance and WHO. Under COVAX, the participating countries including China and USA, and the manufacturers are uniting for the vaccine production. As per the agreement, the countries will receive

the funding upon sharing the vaccine with entire world. The initial aim of the coalition is to produce 2 billion doses of vaccines by the end of 2021 and to have equal access to all countries, even poor nations.

The prominent vaccine candidates that are undergoing clinical trial evaluation in India are Oxford vaccine in collaboration with Serum Institute of India, COVAXIN developed by ICMR-NIV with Bharath biotech, and Sputnik V by Dr Reddy laboratories, and indigenous vaccine by Zydus. Four main producers in China are CNBG of Wuhan, CanSino based in Tianjin, Beijing's Sinovac, and ZFLongkema based in Anhui. Moderna, Pfizer, J&J and GSK-Sanofi have also joined the race for COVID vaccine.

Vaccines can be inactivated whole cell vaccine such as ICMR/NIV/BBLI and SINOVAC or a live attenuated vaccine such as Codagenix/SII (CDX005 nasal vaccine). NVX-CoV2 by Novavax is a novel vaccine based on pre-fusion nanoparticle of spike protein.

Some of the vector borne, nucleic acid and other types of vaccines are listed below:

Vector borne:

- **Adenovirus**: a. Oxford/Astra/SII, b. Cansino
- **Human recombinant adeno virus**: rAd5/rAd6 dual vector (Sputnik V)
- **Measles:** a. Themis (Austria)/SII, b. Zydus, c. Themis (Austria)/MSD
- **Rabies:** Jefferson/BBLI

Nucleic acid:

- **mRNA:** Moderna/NIAID
- **RNA:** Pfizer/BioNtech/Fosun
- **DNA**: a. Symvio, b. Zydus

Others: Coroflu (BBLI), bacteriophage nasal vaccine[3]

BNT162 vaccine by BioNTech-Pfizer

The intramuscular vaccine is being developed by Pfizer along with BioNtech and the efficacy phase 2 trial has been announced. It comprises of mRNA expressing the spike protein receptor binding domain, packed in a lipid nanoparticle. A promising animal-based study in macaque monkey revealed that the vaccine conferred lung protection and induced 10-18 folder higher antibody response compared to human convalescent plasma. The phase 1/2 conducted in 200 subjects, aged 18-55 years, in Germany showed 1.2-2.8-fold higher antibody response than convalescent plasma. The phase 2/3 trial involved 32000 subjects of age group 18-85 years, enrolled in 120 clinical sites in USA, Argentina, Brazil, and Germany. The efficacy reported was around 95% for mild, moderate, and

severe disease forms. However, the major limitation of this vaccine is requirement of storage and transportation facilities at -80 ^{0}C and this will be challenging for developing countries.[4]

mRNA vaccine Moderna/NIAID(USA)

Developed by Moderna in association with NIAID(USA) is a nanoparticle (LNP)-encapsulated, intramuscular mRNA vaccine encoding for a prefusion stabilized form of the spike (S) protein. In phase 1 trial, nearly 120 subjects of age group >18 years were enrolled and 2 doses of vaccine were administered with an interval of 28 days. The vaccine has demonstrated good immune response and stability of 100% with mild to moderate side effects such as fatigue. The vaccine has caused the generation of specific neutralizing antibody in 2-4-fold more titers than convalescent plasma in subjects who received 100 µg. Similar responses were noted in adults >55 years of age. The phase 3 trials involved 30000 subjects at 87 sites in USA, funded by operation Warp speed and BARDA (Biomedical Advanced Research Development Authority USA). Primary end point of this trial was efficacy against symptomatic COVID-19 and safety, and the secondary endpoint was efficacy against severe COVID-19 hospitalization. The efficacy reported for the trial was 94.5%. The vaccine needs -20 ^{0}C storage and can be kept at 2-8^{0}C for 30 days.[5]

Sputnik V Russian vaccine -DRL

This vaccine is invented by Gamaleya Research institute of Russia using modified human recombinant adenovirus vector. It is being developed as a two-dose vaccine using two human recombinant adenovirus vectors namely rAd5 and rAd26, tweaked to carry S protein of SARS-2. The phase 1/2 study involved 76 subjects. In phase 1, rAd26 or rAd5 was used and in phase 2, rAd26 on day 1 followed by rAd5 on day 21. The vaccine was found to be safe and immunogenic, and showed a good T cell response in almost 100% of subjects. Phase 3 trial, involving 40000 subjects across 45 medical centres, has reported an efficacy of 90%. Dr. Reddy's Laboratories has entered an agreement to produce the vaccine in mass scale and to conduct phase 2/3 trial in Indian population. But the challenging part is storage at -20 ^{0}C.[6]

Covishield: Oxford-Astra-SII vaccine

Covishield vaccine uses chimpanzee adenovirus as a vector expressing spike protein S. The study performed by administering single dose in Macaque monkeys showed protection against pneumonia, but not in case of infection. The study in pigs showed boostability of two doses and the phase 1/2 single-blind trial was conducted in 5 centres across UK. In 1077 subjects of 18-59 years age group, subjects who received two doses, 28 days apart, showed good humoral and T cell response. Anti-spike IgG antibody response rose by day 28 with median 157 ELISA units (EU) and was boosted by second dose with median 639 EU. Around 91-100% subjects developed neutralizing antibodies and strong correlation was found between neutralizing Ab and IgG antibodies levels. Local and systematic side effects such as pain and fatigue occurred due to the vaccine administration. Phase 3 trial, carried out in UK, South Africa and Brazil involving 30,000 subjects, revealed that the vaccine found to be

immunogenic in all age groups. Phase 3 trial was conducted in India by Serum institute of India in 17 sites and the company has already produced nearly 5 million doses. This vaccine needs storage at 2-8^{0}C and the efficacy results are expected by December 2020.[7,8.]

Ad5-nCOV: Chinese vaccine (CanSino)

This is a recombinant adenovirus 5 vector S protein vaccine, which is being developed in collaboration with Chinese army. Phase 1 included 108 volunteers with 3 doses and phase 2 trial involved 603 volunteers with low to medium doses. Phase 3 trial was conducted in Saudi Africa over 5000 subjects >18 years age group. Phase 1 and 2 showed reasonable safety, immunogenicity and IFN-γ enzyme-linked immunospot response. This vaccine is only approved for use by Chinese army for 1 year and is not available for public use.

CoronaVac Sinovac

This is a whole cell formaldehyde-inactivated alum adjuvanted vaccine. In animal study conducted in macaque monkey for 3 doses of 0-7-14 days of 3μg or 6μg provided partial or complete protection against severe disease. Phase 1/2 included 600 healthy adults of 18-59 years administered with 2 doses of 3μg or 6μg for 14 or 28 days apart. Good immune response was seen in > 90% subjects with mild side effects and no major safety concern. Phase 3 is underway involving 9000 subjects in Brazil.[9,10]

Whole cell inactivated vaccine

This is a whole cell inactivated vaccine developed at Wuhan, China with formaldehyde inactivated alum-adjuvant. In phase 1, 96 subjects of 18-59 years received 3 doses of 2.5 /5 /10μg for 0-28-56 days apart. Phase 2 conducted by administering 2 doses of 5μg for 14 or 28 days apart demonstrated mild to moderate side effects. Phase 3 trial is underway in Peru, Morocco, and UAE.[11]

Covaxin: BBLI-NIV-ICMR vaccine

Bharat Biotech has tied up with ICMR and NIV to develop a whole cell inactivated vaccine. Animal study done in macaque monkeys revealed that the vaccine prevented pneumonia and demonstrated good viral clearance. Phase 1 involved 375 subjects of 19-55 age group who were given 2 doses for 14 days apart. Phase 3 included 750 subjects of 12-65 age group who received 2 doses for 14 days apart.

NVX-CoV2373 vaccine by Novavax (SII)

It is a prefusion protein nanoparticle-based vaccine. The phase 1 conducted on 130 healthy subjects of 18-59 years at two sites in Australia for 2 doses (at 0-21 days) demonstrated mild side effects with

no safety concern. Phase 2b involved 2665 subjects with 240 HIV +ve patients in South Africa. Phase 3 was conducted among 10,000 subjects in UK and 27000 subjects in USA.[12]

Ad26-S protein vaccine by Johnson & Johnson

It is a monovalent vaccine comprising of replication incompetent Ad26 vector. The studies conducted in monkeys revealed that the vaccine conferred good protection. Phase 3 trial is ongoing with 60,000 subjects in USA and other sites.[13]

ZyCoV-D vaccine by Zydus

It is a non-replicating, non-integrating DNA plasmid vaccine targeting the viral entry protein of COVID-19 virus. Phase 1/2 involved 1000 healthy volunteers at a single site in Ahmedabad. Phase 2 is yet to begin soon.

Other COVID-19 vaccines

- Subunit vaccine with adjuvant by Sanofi/GSK
- Measles vector-based vaccine by MSD.
- Nasal vaccine such as Waterloo, SII, and altimmune
- Oral vaccine (Vaxart)

FAQ on COVID vaccine and answers

1. Whether COVID-19 vaccine does not work at all?

Three vaccines have already proven >95% efficacy and some are in final stage of clinical trials.

2. If COVID-19 virus mutates and escapes antibody prophylaxis?

So far, there is no information regarding the incidence of any significant mutation of virus that leads to severe second wave, despite an antibody prophylaxis.

3. If COVID-19 vaccine leads to ADE?

No major cases of ADE have been reported in > 30,000 of the subjects who participated in phase 3 trial.

4. COVID-19 may disappear by the introduction of the vaccine?

COVID-19 is here to stay for years, despite the introduction of the vaccine.

5. Whether COVID-19 becomes mild over years?

COVID-19 may become milder over years.

6. Who will receive the first vaccine?

The frontline healthcare workers, people with morbidities and elderly will be receiving the vaccine first.

7.Whether the poor nations receive the vaccine?

COVAX*, co-led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO has assured that even poor nations will receive the vaccine.*

8. Who will fund the vaccine?

Funding will be given by governments, bilateral and multilateral organizations, NGOs, and the private sector.

Conclusion

Since vaccine cannot be considered as a magic bullet, returning to normalcy requires the widespread acceptance and adoption of precautionary interventions such as masking, hand hygiene, social distancing, and prompt testing. Both droplet and aerosol spread has been confirmed for COVID virus, hence social or physical distancing is important to prevent transmission. Sanitization of both the hands and surfaces is crucial to prevent fomite transmission.

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FEVER FOUNDATION

Vision

Strive towards imparting knowledge on the unmet needs and provide information on research, education and therapy updates on fever management.

Mission

- Independent, non-commercial foundation supporting the educational / academic activities to address the unmet needs in fever management
- The foundation is committed to conceive, build and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals
- To run patient education programs on fever management

Objectives of Fever Foundation

- To address the unmet needs and provide updates on fever management
- To provide access to health care through evidence based programs that can reach to large audience
- To engage eminent doctors for various scientific activities

MICRO KNOWLEDGE ACADEMY