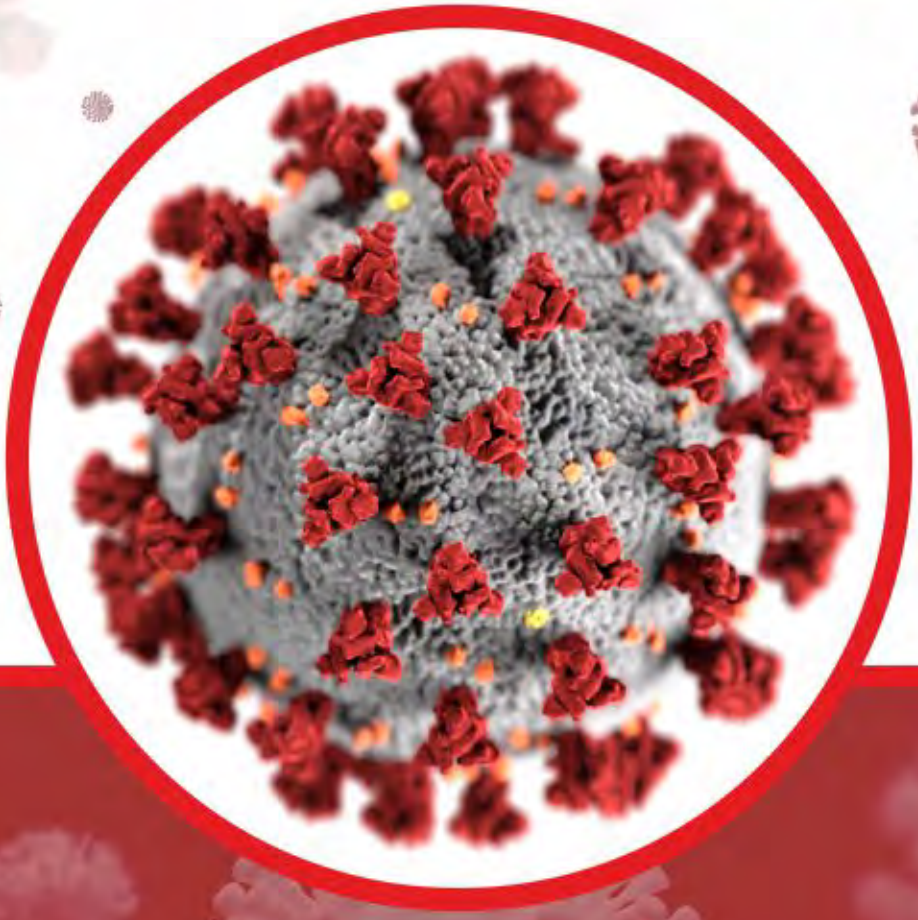
Management of Covid 19

A Handbook For Family Physicians



Dr. Alok Sharma, Dr. Hemangi Sane, Dr. Nandini Gokulchandran,
Dr. Balaji Tuppekar, Dr. Prakash Gote, Ms. Pooja Kulkarni

A NeuroGen DCH & KLS Wellness Institute Publication
Navi Mumbai, Maharashtra, India.

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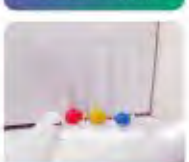
Gut Cleansing



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- Neurovascular conditions Stroke & Dementia
- Neurodevelopmental disorders Autism & Cerebral Palsy
- Neuromuscular conditions Muscular Dystrophy & Motor Neuron Disease

Management of COVID-19

A Handbook for Family Physicians

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Management of COVID-19

A Handbook for Family Physicians

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This book is basically a compilation of information / literature on the available on the topic, from various sources (which have been acknowledged duly). However, this is by no means an exhaustive resource, since the field is evolving at a very rapid pace. Every effort is made to ensure accuracy of material, but the publisher, printer and author will not be held responsible for any inadvertent error(s).

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सबका साथ, सबका विकास, सबका विश्वास
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जय अनुसंधान

सत्यमेव जयते

डॉ हर्ष वर्धन
Dr Harsh Vardhan

स्वास्थ्य एवं परिवार कल्याण, विज्ञान और प्रौद्योगिकी व पृथ्वी विज्ञान मंत्री, भारत सरकार
Union Minister for Health & Family Welfare, Science & Technology and Earth Sciences Government of India

Message

I am delighted to know that Dr Alok Sharma has compiled a book titled **"Management of COVID-19", A Handbook for Family Physician.**

This book gives a detailed description of COVID-19 case management and preventive care at various levels along with some futuristic vision of COVID-19 treatment.

I congratulate Dr. Alok Sharma and his team for editing this book. I hope that this book will provide an effective learning experience to Family Physicians leading to an improved patient care.

I extend my best wishes for their future endeavours.

(Dr. Harsh Vardhan)

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Dr. Alok Sharma, *MS, Mch*

Dr. Alok Sharma is a Neurosurgeon and is presently the [a] Professor & Head of Department of Neurosurgery at the LTMG Hospital & LTM Medical College in Sion, Mumbai as well as the [b] Director of the NeuroGen Brain & Spine Institute in Navi Mumbai [c] President of Indian Society of Regenerative Science (ISRS) and [d] Vice President International Association of Neurorestoratology (IANR) He completed his graduate and post graduate studies from the Seth G.S. Medical College and KEM Hospital of Mumbai University. Subsequently he did Trained Overseas in Sweden, England, Germany, USA, & Japan. He has written/edited 20 books, has over 150 scientific publications in medical journals and has made over 200 scientific presentations in India and overseas. He has been conferred with numerous honors and awards in his distinguished career. He has dedicated his life to doing research on incurable disease and injury of the brain and spine and to providing the latest and most advanced treatments for patients who are paralyzed and disabled from incurable neurological conditions. Is the pioneer of Stem cell therapy in India.

He setup the Stem cell and Genetic research laboratory at the LTMG hospital & LTM Medical College which was the first of its type in Mumbai. He has also created India's first dedicated Stem Cell Therapy and Neurorehabilitation center in Navi Mumbai. He is a staunch believer that Stem cell therapy can relieve a lot of human suffering of neurological patients and makes every attempt to popularize this new approach amongst the medical community. His special interest in Neurosurgery are Stereotactic and Functional Neurosurgery, Psychosurgery, Neuroendoscopy, Spinal Fixations and Surgery for Cerebral Ischemia. He has a special personal interest in Neurobiology of the mind and lectures extensively on the relationship of the brain/mind to health and disease. He is a strong advocate of the role of yoga, meditation, natural therapy and diet in the prevention of various modern illnesses.

Contribution during Covid 19 pandemic

(A) Scientific research

1. Dr Alok Sharma got approval for the first DCG(I) approved, CTRI registered clinical trial on the use of Mesenchymal Stem cells in Covid 19. This trial is currently ongoing, showing good safety and satisfactory efficacy.
2. Dr. Alok Sharma also completed India's first CTRI registered clinical trial on the use of IV Ozone in Covid 19.
3. He completed a study on role of IV ozone as prophylaxis for healthcare workers (HCWs) in a dedicated Covid Hospital. The results have been accepted for publication in European Review for Medical and Pharmacological Sciences.
4. He has completed a comparative study comparing outcome of conventional treatment and conventional treatment combined with IV ozone in 680 Covid-19 patients.

(B) Clinical Service

1. Dr Alok Sharma volunteered to have NeuroGen Brain and Spine Institute of which he is the director, to be converted into a dedicated Covid Hospital from June 2020 onwards where a total of 900 patients were treated.
2. Presently, he is involved in studying post Covid sequelae and offering a comprehensive treatment plan for post Covid.

Dr. Hemangi Sane, *M.D. (Internal Medicine, USA) (Medical Physician)*

Dr. Hemangi Sane is Deputy Director and Head of Research and Development, Consultant Physician at NeuroGen Brain and Spine Institute, Navi Mumbai. She acquired MBBS degree from esteemed G S Medical College more than 20 years ago. Dr.Sane has completed her MD from the renowned New York Medical College and has 10 years of clinical experience as an Internal medicine physician in USA. She has been recognized as one of the 'Leading physicians of the world' by The International association of Internists, USA. In 2013 she was awarded the International Women's day award by the Mayor of Mumbai. Women Economic Forum has also presented her as the "Iconic Women Creating a better world for all" She is the founder of Asha Ek Hope foundation for ALS/MND, India.She is certified in Precision and Anti-aging medicine from USA. She has more than 90 scientific peer reviewed publications to her name in the field of stem cell therapy. She has co-authored more than 12 medical books, along with multiple chapters in various International Medical Books. In Covid-19pandemic she played a vital role in hospital management of more than 500 Covid patients. She was also Incharge ofCovid Prevention Management of Health Care Workers at NeuroGen. She was also involved in clinical trials for Covid-19.

Dr. Nandini Gokulchandran, *M.D. (Regenerative medicine consultant)*

Dr. Nandini Gokulchandran is an M.D. in medical Microbiology, presently working in the capacity of Deputy Director & Head of Medical Services at Neurogen Brain and Spine Institute. She did 4 years of post graduate fellowship in the field of Developmental Neurobiology and stem cell research at Tata Institute of Fundamental Research, Mumbai. She brings to NeuroGen Brain and Spine Institute an astute amalgamation of medical/clinical background with deep faith in and understanding of stem cell research & regenerative medicine, especially in neurodevelopment disorder such as autism, cerebral palsy & mental retardation. She has to her credit 97 scientific publication in international peer review journals (1st Author publication in reputed Science magazine as well as 7 papers on autism). She has also co-authored 18 books on stem cell therapy and neurological disorders.

Dr. Balaji Tuppekar

Completed post-graduation in 2016 from prestigious institute B. J. Government Medical College and Sassoon Hospital, Pune. Completed post PG one year bond from Government Medical Nanded. Working as Assistant Professor in Department of Pulmonary Medicine at D Y Patil Medical College and hospital Navi Mumbai since 2018. Also, a Consulting pulmonologist & bronchoscopist at Navi Mumbai and consulting chest physician at Neurogen Brain and Spine Institute, Navi Mumbai. Has experience of more than 10 years.

Dr. Prakash Gote

Completed MBBS from GMC, Nagpur. Did anaesthesia from Terna Medical College. Worked as consultant intensivist at Kohinoor Hospital, Kurla, Mumbai, Worked as consultant intensivist and Anaesthetist at MPCT hospital, Navi Mumbai. Has experience of more than 10 years.

Pooja Kulkarni

Ms. Pooja Kulkarni is the Chief Research Officer at NeuroGen Brain and Spine institute, Navi Mumbai. She has completed MSc in Biotechnology from Mumbai University. Her interest is in clinical research involving cell therapy and she is actively involved in the same for 10 years. She has more than 60 scientific peer reviewed publications in national and international journals. She has been the Scientific and Research Co-ordinator of 12 books and has co-authored 2 books in the field of stem cell therapy and rehabilitation.

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Ms. Darshita Salian
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PREFACE

When the Navi Mumbai Municipal Corporation requested us to convert our neurological hospital into a Dedicated Covid Facility, we gladly took on the responsibility.We realised that it was our time to serve our city, our state and our country. Never before in our living memory has something as small as a virus completely brought mankind to its knees. Life as we know it, has fundamentally been changed and if we have to get back to our previous way of living, it is important that we win this epic battle against the Covid virus.

We started working as a Dedicated Covid Hospital in the first week of June 2020, and since then have treated over 800 patients. Ours was a 75 bed facility which includes 20 ICU beds. It wasn't easy for us to shift from a functioning neurological institute to a Covid institute. There were infrastructural changes that had to be made such as creation of intensive care units, central supply of oxygen to the entire hospital, creation of isolation and triage areas and dividing the hospital into red, orange and green zones. But, more important than the infrastructural changes, were the changes that we had to bring about in the thoughts and attitudes of the staff. It was very important that our staff was motivated and inspired and wanted to do this work rather than having to do this work forcefully. In normal regular medical practice, the staff is very comfortable because all they have to do is look after the patients. But in the Covid facility, apart from looking after the patients, they also have to look after their own health. So, the first step in getting our team prepared was to get rid of fear and the best way to get rid of fear is to have information and knowledge. Because when one is weaponised with knowledge, one can take sensible precautions and can protect one's self. As we have treated these patients, we have learnt a lot and we have also learnt that it is important that family physicians and doctors all over have appropriate knowledge. Since, Covid is just a disease that has evolved in the beginning of this year, there are no dedicated books for Covid, there isn't enough literature on Covid and most of the knowledge that people have comes from WhatsApp forwards. We believed it was important that all the relevant knowledge which was scientific and validated, was put together in a simple book which would inform our family physicians about what to do when they were faced with a suspected Covid patient.

We will now have to learn to live with the epidemic and slowly there will be no more Dedicated Covid Hospitals and patients of Covid will be treated at home and most likely will be treated by family physicians. Understanding how the disease evolves, understanding how the medicines that are being used for it

work, will be very important in getting a control over the disease and saving lives.

We have attempted to put together all the relevant information from scientific journals, books and other sources as well as put in our own experiences into this book. We must state however, there are still no definite cures or no evidence based definitive approved treatments for Covid. All the treatments that are currently being used and most of what have been described in the book have been tried out by different doctors and found to be useful in some cases and successful in others. So, the knowledge in this field is constantly evolving and what we have put in this book is what was relevant at the time of its publication. This knowledge will constantly keep on changing and it is very important for those readers of the book to know that whatever is in this book was relevant at the time of its publication and that in later months or years there may be other newer treatments, other drugs, other treatment modalities that may become more relevant or get approved. So our purpose is just to put together all the knowledge and information we have in an easily readable format. We wish you all a happy and informative reading!

Dr. Alok Sharma
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CLINICAL & RESEARCH CONTRIBUTIONS OF NEUROGEN DCH & KLS INSTITUTE TOWARDS COVID 19

(A) During the Pandemic

1. From June 2020 onwards NeuroGen Brain and Spine Institute was converted into a Dedicated Covid Hospital (DCH) called as "NeuroGen Dedicated Covid Hospital". It was a Navi Mumbai Municipal Corporation (NMMC) designated Covid hospital with total **75 beds** which included **20 ICU beds**. In total over **900 Covid patients** were treated in this hospital. Special services offered apart from regular clinical treatments were personalised counselling , Physiotherapy and other rehabilitation and special digital communication efforts for the patients and families.

2. Healthcare workers welfare during COVID management: Along with treating Covid patients, NeuroGen also empowered their healthcare staff by providing free prophylactic treatment which included immunity kit (HCQ and vitamins) and steam inhalers. IV Ozone was also offered to all staff as a prophylaxis.

(B) Research contributions of NeuroGen in COVID :-

1. NeuroGen sponsored and is conducting **India's first DCG(I) approved, CTRI registered** Phase 1 clinical trial of **intravenous administration of mesenchymal stem cells in patients with novel COVID-19**. This trial is currently ongoing and is showing good safety and efficacy.

2. NeuroGen completed India's **first CTRI registered clinical trial** on the use of **IV Ozonised saline** as an adjuvant treatment **in Covid 19 patients**. Publication of this study is under process.

3. NeuroGen completed a study on **role of IV Ozonised saline** as additional **prophylaxis for healthcare workers (HCWs)** in a dedicated Covid Hospital. The **results have been accepted for publication** in pubmed indexed international journal **"European Review for Medical and Pharmacological Sciences".**

4. NeuroGen also performed a **comparative study** comparing outcome of conventional treatment vs conventional combined with IV ozonized saline treatment in **total 680 Covid 19 patients**. Study analysis is ongoing.

5. NeuroGen has published **2 books** on Covid 19 of which one focuses on clinical intervention and second focuses on the basic science and pathophysiology of Covid 19.

   (i) Management of Covid 19- A Handbook for Family Physicians

   (ii) Cytokine storm in Covid 19

(C) Post Covid Contribution

1. **KLS Wellness Institute :** KLS Wellness Institute has initiated a **study on post Covid sequelae** in Treated Covid positive patients and is also offering a **comprehensive** integrative medical **treatment plan** for post Covid patients.

2. **NeuroGen: Approved** by Government of India for administration of **Covid Vaccine.**

Clinical work at NeuroGen DCH

Principal authors at NeuroGen DCH

With patients in the ICU

With adult patient in routine isolation room

With pediatric patient in routine isolation room

Individualized counselling of patients at discharge

Disclaimer

Since Covid-19 is a new illness, there are no definitive evidence-based treatments available as of date. The current treatment practices are all based on physician's experiences and commonly held beliefs of best practices.

The treatments in this book are based on our experience of treating patients when we were a Dedicated Covid Hospital as well as information available in the public domain from other doctors, hospitals, international and national agencies.

The information contained in this book is current as on the date of publication and this is likely to change as new evidence-based information evolves. This information is meant to serve as a guide and this book does not claim any of the treatments mentioned to be a standard of care. Readers are recommended to keep themselves updated with the most recent scientific publication and advisories from various agencies and government bodies.

Section A

About Covid

01 Introduction Chapter for Book Management of COVID for family physicians

In the year 2020, the COVID-19 Pandemic flooded the globe like a tsunami, took over the health care system by surprise and has now finally settled down to a gentle rhythm with occasional turbulence. However, the threat of second and third waves still looms large beyond the horizon.

The initial six months saw the shutdown of smaller clinics and overwhelming of the critical care facilities of the hospitals.

Even those health professional and health care facilities who had never in their lives treated patients in acute care settings had to reinvent themselves.

Basic medicine professionals, paramedics, rehabilitation experts shouldered the responsibilities of taking care of patients alongside and under intensive care specialists and chest physicians.

Having learnt on the job and practically jumped into turbulent waters, now, we, the health care professionals are finally equipped to sit down and take stock of that was and is "the COVID-19 Pandemic".

The following is the current situation:

1. We are hopefully over the worst.
2. We have gained many learnings which we can now put into semblance of "must know", "not needed to know" at the grass root level.
3. The vaccine delivery is on the roll now.

4. It is time to equip and empower the grassroot health care system, viz, the family physician with knowledge about the SARS COV2 virus, how to distinguish COVID-19 from a seasonal flu , care to be taken at home and at what point to shift to an IPD settings.

A suspected COVID patient is the one who may meet the epidemiological and clinical criteria specific to COVID-19. Family physicians are the first to be contacted if an individual notices any common symptoms of COVID-19. They see a large number of patients with viral fever. However, COVID-19 is a new disease and its epidemiological pattern is still uncertain. It is also difficult to differentiate COVID-19 solely on the basis of its symptoms. COVID-19 should not be mistaken with normal flu syndrome. Hence, the role of a family physician is of utmost importance in distinguishing COVID-19 from other flus and making timely decisions regarding management of the suspected individual. Early detection of COVID-19 can prevent patients from developing severe irreversible symptoms for which there may be a requirement of intensive care or highly invasive procedures such as intubation and mechanical ventilation, which currently results in a high mortality rate. In order to break the chain of transmission, it is important to isolate every suspected or confirmed case, provide appropriate treatment and trace their contacts at the earliest.

The presentation of COVID-19 is varied. The joke in the medical fraternity is that, except for fracture and pregnancy, COVID-19 can present in any form.

So, does that mean that any patient who comes into your practice should be a COVID19 suspect??

Does everyone have to be tested for COVID-19?

What history needs to be taken?

What tests need to be carried out?

Detailed history is very important. You need to spend time to understand the spatio – temporal scenario.

- Previous history – repeated infections / allergies
- Exposure to COVID-19 in family, friends, colleagues, domestic help
- Attended any social functions

- How do they travel to work, etc

- Comorbidities such as HTN / DM

- Other Symptoms:

  - Anosmia (sudden loss of smell) is a classic symptom seen in the most patients. If this history is not given spontaneously by the patient or if helpline is doubtful due to blocked nose – do the testing yourself.

  - Loose motions, myalgia, malaise

  - Often above symptoms are attributed to "indigestions", "food poisonous", "have eaten outside food"Or "Haven't slept properly", "Too much work".

In the scenario of the pandemic, it is important to take these symptoms seriously, but equally important, "NOT TO PANIC".

WHY IS IT IMPORTANT TO TAKE THESE SERIOUSLY?

1. We are used to seasonal flus, allergies, cough and cold. For the general population, these ailments, just mean taking medicines for an average 3 – 4 days and back to work. Sometimes, viral malaria may lead to 1 – 2 weeks of lethargy.

2. In the background of COVID-19, this flu, is likely to

   a. Affect the whole family

   b. Cause debilitating pneumonia and other complications in elderly, those with co-morbidities and compromised immune system.

3. The infective period of COVID-19 is still considered to be an average of 14-17 days. Hence, effectively one is off work and at home for close to two weeks.

So, what would be a pragmatic approach to COVID-19, as the pandemic is loosing its steam

- As a Family Physician, you need to make a clinical judgement to differentiate whether a certain symptom indicates if it is a viral fever, seasonal fever/ dengue, malarial fever.

- Basic Dictum should be

  (a) Isolate- assuming it is an infectious and contagious condition. Keep away from elderly and vulnerable people.

  (b) Prescribe a combination of antipyretics, antihistamines, multivitamins, antibiotics, etc

  © Monitor temperature and saturation. Tell patient to inform the Family Physician twice a day. Red flag- any sign of breathlessness or persistent fever. Such patients should be tested for COVID-19 and referred for admission. Please note that the 2nd week post fever or vague symptoms, is the most critical in COVID-19. Hence, monitoring for 2 weeks is critical.

  (d) Do a basic blood workup i.e CBC and CRP.If fever present rule out malaria and Dengue A raised neutrophil count with a lowered lymphocyte count in the background of normal TLC and a raised CRP should be followed up closely (Probable COVID-19).

  (e) The elderly and highrisk patients with pyrexia of unknown origin, respiratory symptoms, vague history and bodyache, malaise, loose motions should be tested for COVID-19 and then referred for admission to an indoor facility.

The Rule of thumb to be followed:

1. When in doubt, check for SARS-CoV2

2. It is better to over diagnose than under diagnose.

This book gives detailed information about every aspect of COVID-19 from diagnosis to treatment to recent advances in the field which will help timely detection of COVID-19 and prevent severe symptoms associated with it.

Questions to Ask:

1. Any exposure to COVID-19 in family, friends, colleagues, domestic help, etc?
2. Attended any social functions?
3. Any travel history?
4. What are the symptoms?
5. Any Co-morbidities?

Examinations to be done:

1. Temperature with Digital Infrared Thermometer
2. Oxygen saturation using Pulse oxymeter
3. General examination and chest auscultation, if required to be done taking all precautions

Investigations to ask for :

1. qRT-PCR/Rapid Antigen Test
2. Laboratory tests such as CBC, ESR, CRP, D-Dimer, LDH, etc
3. Chest Xray/ High Resolution CT scan

When to treat yourself and when to refer to Covid hospital

COVID-19 positive patients presenting with mild symptoms, uncomplicated upper respiratory tract infection with no evidence of hypoxemia or breathlessness, oxygen saturation (SpO2) of ≥ 94% in room air and a respiratory rate (RR) ≤ 24/minute can be isolated at home and treated by a family physician.

However, if the patient is above 65 years of age, has comorbidities such as diabetes mellitus, hypertension, cancer, etc. and/or is clinically mild with possibility of progression, moderate or severe in their presentation should be referred to a Covid hospital.

Treatment recommended for mild asymptomatic patients at home

Sample Prescription

Rx

1. Tab HCQ 400 mg po 1-0-1 on Day 1. Followed by 200mg 1-0-1 x 4 days. (Take with meal) (Not for cardiac abnormalities) *
   *if patient has ECG/ cardiac abnormalities not to give HCQ
2. Tab Doxycycline 100 mg po 1-0-1 x 7 days
3. Tab Ivermectin 12 mg po 1-0-0 x 3 days
4. Tab Pantoprazole and domperidone 40mg po 1-0-1 x 5 days
5. Tab Vit C 1 gm po 1-0-1 x 15 days
6. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
7. Tab Zinc 50mg po 0-1-0 x 15 days
8. Tab Magnesium 500mg po 0-1-0 x 15 days
9. Tab Selenium 100 mcg po 0-1-0 x 15 days
10. Tab Multivitamin po 0-1-0 x 15 days
11. Syp Vit D3 60K po once a day x 3 day. Then once a week for 4 weeks
12. Cough syrup po 1-1-1 x 7 days
13. Tab Paracetamol 500mg SOS for fever
13. Steam inhalation 4 times a day
14. Ayush Kadha daily for 7 days

** If patient has cough, add
#Tab Azithromycin 500 mg po 1-0-0 x 5 days OR
Tab Amoxicillin/Clavulanate 625 mg po 1-0-1 x 7 days

#Note: when combined with HCQ there is risk of QT prolongation so, this combination is to be avoided in patients above 60 years and with cardiac history.

02 Pandemic and Challenges

Coronavirus disease 2019 (COVID19) pandemic, caused by SARS-COV2, is of unprecedented global public health and socio-economic crisis. It is one of the greatest global crisis since World War II. One of the first cases of COVID-19 was reported on 17 November, 2019 in Wuhan, China. On 31 December, 2019 the Chinese authorities reported the outbreak to the World Health Organization (WHO)for which an investigation was launched in January, 2020. On 30th January, the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC).

From the outbreak in Wuhan, the virus has spread throughout the world to every continent rapidly. The preparedness and response to the crisis of all countries to the pandemic has been varied.

Currently, 112 million cases have been affected worldwide and 2.49 million have died. Whereas, in India, 11 million cases have been detected with Covid and 1,57,000 have died.

The economic impact of this pandemic is likely to be more in developing and underdeveloped countries. This may lead to increased poverty, worsened socio-economic inequalities affecting health and nutrition indices and cause disruptions in health services. These may have long-term associations with health indicators. Morbidity and mortality due to COVID19 is largely attributed to co-morbid conditions such as diabetes, hypertension or cardiovascular disease which are rampant in countries like India.

The pandemic can be divided into three phases,

1. Phase one: Wherein social distancing, shutdown and general measures of hygiene in order to contain and mitigate the spreading of the infection and flatten the curve of new cases over time is enforced

2. Phase two: The curve reaches the highest incidence of new cases, and mortality rate peaks, including a plateau phase.

3. Phase three: recovering from the pandemic, which requires re-organizing and re-establishing services and practices.

Challenges of the pandemic

The government of most countries worldwide enforced a complete lockdown which has caused a serious setback with respect to the economy alongwith physical and mental health.

- The economic slowdown could aggravate malnutrition.

- The loss of daily wage earnings or joblessness can make it difficult to buy essentials

- Whereas, the lockdown could also be a cause of weight gain because of poor physical activity, increased snacking and consumption of calorie-dense foods.

- Weight gain and obesity may increase the risk of development of diabetes and cardiovascular disease in the future.

- Increase in chronic stress, anxiety, depression, alcohol dependence, self-harm and increased domestic violence could also be a consequence of the lockdown

Challenges for medical system

- The Covid pandemic has been extremely challenging for the health care system worldwide.

- There has been a shortage of workforce and poor infrastructure with respect to hospital beds, equipment, etc which has affected the quality and availability of timely care to patients.

- Lack of adequate infrastructure makes it extremely difficult to contain the COVID-19 transmission

Challenges for Family Physician

- GPs are the first medical practitioners whom the patients will visit after onsent on symptoms.
- A Family Physician is involved in diagnosing, treating patients and educating them
- The main challenges a Family Physician can face are overwhelming numbers of patients, exposure to infectious risks, the uncertainties and unknowns about the trajectory of the disease, and coping with fears and panic among the patients

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03 SARS-COV-2 Structure and Invasion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new strain of coronavirus, discovered in Wuhan, China, in December 2019, which is the cause of the current global pandemic COVID-19. Its full genome was sequenced by Shi Zhengli, a coronavirus expert at the Wuhan Institute of Virology. The virus was initially referred to as "novel coronavirus 2019" (2019-nCoV) by the WHO but was later renamed as SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

Structure of SARS-CoV-2

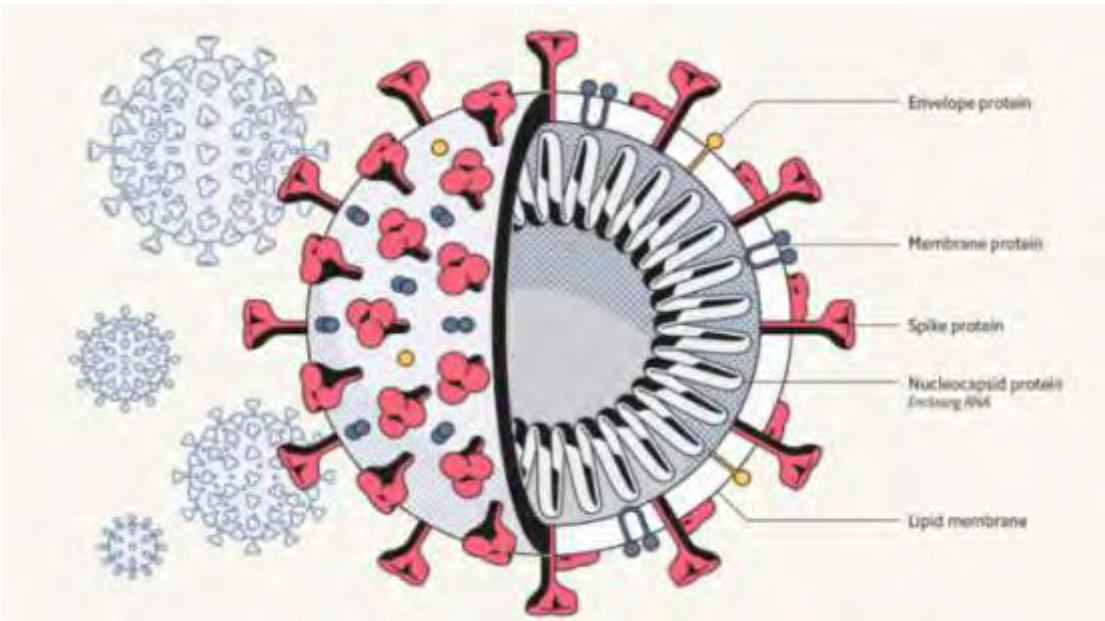

Fig 1 - Structure of SARS- CoV-2

Coronavirus mainly belongs to the family Coronaviridae of which SARS-CoV-2 is classified as a Betacoronavirus which usually infects the mammals. They are typically spherical, fatty enveloped viruses, which encapsulate large single-stranded RNA genomes typically ranging from 27 to 32 kb. The genome is packed inside a helical capsid formed by the nucleocapsid protein (N) and further surrounded by the envelope.

Coronaviruses have characteristic spikes protruding from its surface. SARS-CoV-2 contains four structural proteins (spike, envelope, membrane, and nucleocapsid) and single-stranded RNA. The spikes help the virus to bind to a receptor and facilitate host cell entry. It comprises two subunits; S1 subunit-responsible for binding to the host cell receptor and S2 subunit- responsible for fusion of the viral and cellular membranes. They have a high-affinity towards binding to human ACE2 receptors and a functional polybasic cleavage site at the junction of the spike protein's S1 and S2 subunits which enhances spike protein cleavage and increases viral infectivity.

The RNA genome consists of 29,903 nucleotides wherein, one-third of the genome consists of genes for the four structural proteins and eight genes for accessory proteins that inhibit host defenses. Most of the remainder of the genome consists of the replicase gene, which encodes two large polyproteins that are cleaved into 16 nonstructural proteins (NSP) that assist in replicating and proofreading the viral genome

Invasion

SARS-CoV-2 attaches to human cells with glycosylated spike protein and binds with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells. Specifically, the receptor-binding domain (RBD) of the spike protein mediates recognition of the ACE2 receptor. These receptors are present throughout the body on organs such as lungs, heart, liver, intestines, kidneys, etc. Once the virus has attached to the ACE2 receptors, the TMPRSS2 protease cleaves the spike protein to expose a fusion peptide. The viral membrane then fuses with the host cell membrane. In addition to mediating virus entry, the spike also causes host immune responses.

Virions are then able to enter and release their RNA into infected cells, where it is replicated and translated into new viral proteins. Nucleocapsid proteins bind to RNA molecules and are then encapsulated by the envelope, spike, and membrane proteins to form new virions. Infected cells can produce 100 to 1,000 virions per day.

Since the ACE2 receptor is widely distributed on the human alveolar type II cells and capillary endothelium, lungs are particularly susceptible to the SARV-CoV-2 infections which may lead to permanent changes to the lung function.

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04 Disease Progression and Cytokine storm

Disease Progression

The spike proteins on SARS-CoV2 initiates infection by binding angiotensin-converting enzyme (ACE)-2 receptors on human cells. Covid infection occurs in three stages.

Stage 1 Early infection phase: the virus multiplies inside the body and is likely to cause mild symptoms of upper respiratory tract infection similar to that of common cold or flu.

Studies have shown that the median incubation period, the time between infection and the onset of symptoms, is 5.2 days, but it can be as long as 14 days in some cases. In some patients, infection worsens rapidly and patients progress to phase 2 the end of the first week or the beginning of the second week.

Stage 2 Pulmonary phase: The immune system is strongly affected due to infection which leads to pneumonia alongwith typical respiratory symptoms such as cough and shortness of breath. Blood clotting may also occur in this phase of infection.

This phase is further divided into Stage IIA wherein pneumonia is not accompanied with hypoxia and Stage IIB wherein pneumonia is accompanied with hypoxia and the patient may require hospitalization and oxygen supplementation. Patients in this phase of the disease may deteriorate quickly to the hyperinflammatory phase.

Stage 3 Hyperinflammatory phase: There is an exaggerated inflammatory

response which is the main cause of acute lung injury or its severe form ARDS and multi-organ failure in COVID-19. Patients with ARDS usually require mechanical ventilation in the intensive care unit (ICU).

Cytokine Storm

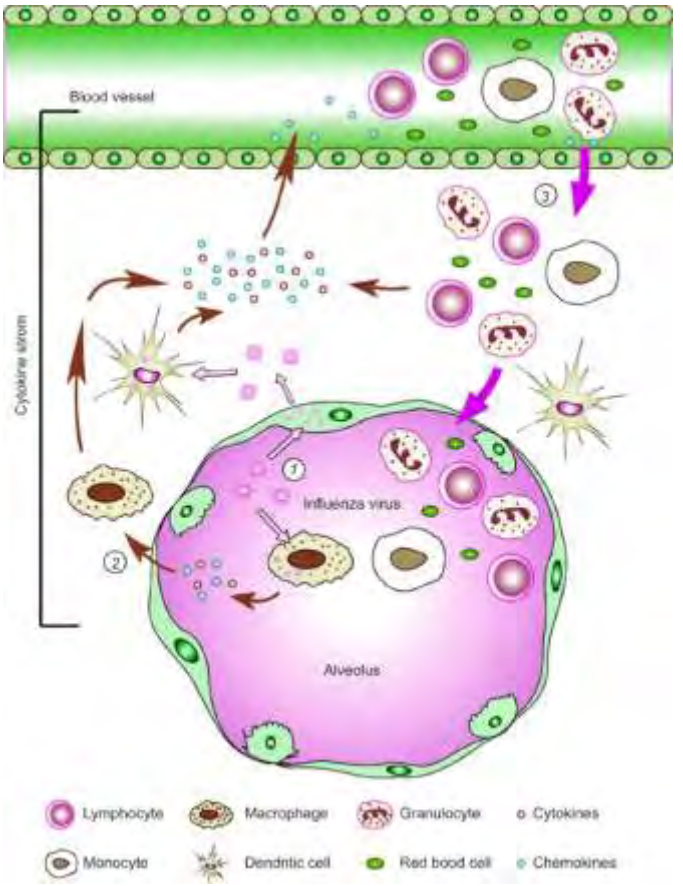

Fig 1 - Cytokine Storm

The exaggerated or hyperinflammatory response is also known as "cytokine storm" which leads to release of a large amount of pro-inflammatory cytokines. Studies have shown that patients with COVID-19 have high levels of inflammatory cytokines, such as interleukin (IL)-1β, IL-2, IL-6 IL-7, IL-8, IL-9, IL-10, IL-18, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, fibroblast growth factor, macrophage inflammatory protein 1, compared to healthy individuals.These cytokines are produced by immune cells such as macrophages, dendritic cells, natural killer cells and the adaptive T and B

lymphocytes. Influx of these immune cells at the site of infection cause destructive effects on tissues resulting from destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure, and ultimately death.

Furthermore, viral entry into the host through ACE-2 receptors interrupts angiotensin II (AngII) metabolism which results in an initial increase in local AngII concentrations that may enhance proinflammatory cytokine release and stimulate microvascular dysfunction and a prothrombotic milieu.

Studies have demonstrated higher baseline NLR, ESR, CRP, Ferritin, IL-6, D-dimer levels in progressive patients which may be associated with inflammatory response and cytokine storm induced by virus invasion.

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05 Complications of COVID-19

SARS-CoV-2 infects the human cells via angiotensin-converting enzyme 2 (ACE2) receptor. These receptors are present on lungs, liver, kidneys, gastrointestinal tract, vascular endothelial cells and arterial smooth muscle cells. Respiratory system might be the primary system affected in SARS-CoV-2. However, all these organ systems may also be affected due to high expression of ACE2 receptors. This further complicates medical management and adversely affects clinical outcomes of patients infected with COVID-19.

Factors such as age, underlying comorbidities such as diabetes, hypertension, cardiac conditions, respiratory conditions, cancer may challenge the medical management and increase the risk of fatality in Covid patients. 1 out of 6 patients experience complications which are mostly associated with cytokine storm.

Most observations suggest that the devastating complication of COVID-19 may not be a typical pneumonia or ARDS, but rather a dysfunction in blood oxygenation. COVID-19 complications may include the following.

Acute Respiratory Failure (ARDS)

ARDS is defined as acute hypoxemic respiratory failure following an acute event (such as a respiratory viral infection) that presents as bilateral pulmonary infiltrates on lung imaging in the absence of a purely cardiogenic or hydrostatic etiology. ARDS due to COVID-19 causes diffused alveolar damage in the lung. As a result, oxygen transport into the bloodstream reduces and patient may need supplementary oxygen or mechanical ventilator to breathe. As patients

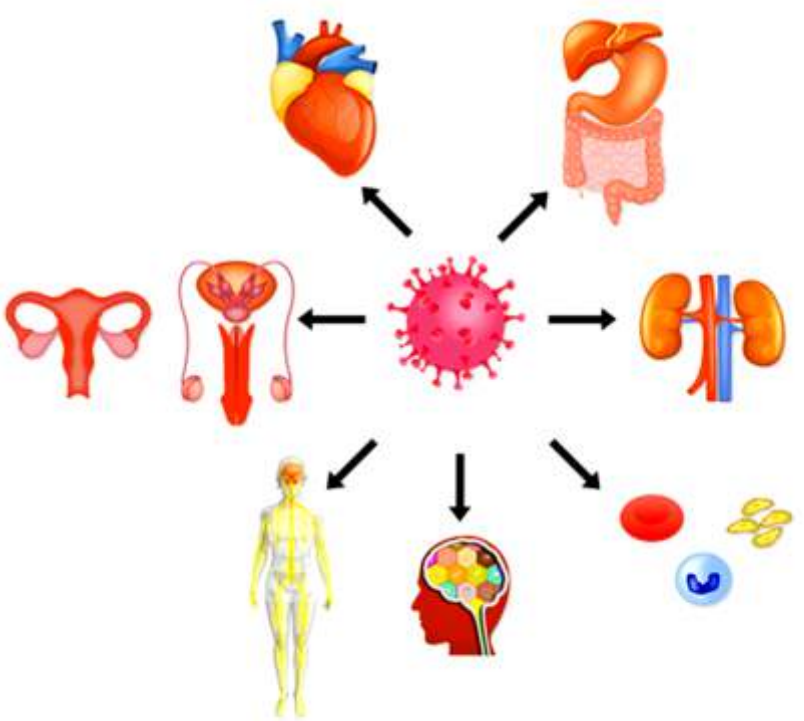

Fig 1 - Complication of COVID

with COVID-19 move through the course of their illness, lung fibrosis is reported as one of the long term effects of ARDS since during the healing process, there is formation of fibrous lesions with gradual replacement of cellular components by scar tissues. ARDS is the leading cause of death in COVID-19.

Acute Liver Injury

Liver injury occurs mostly in critically ill patients with COVID-19, who have other coexisting causes of liver damage.Studies have shown that levels of liver function tests, such as serum transaminases, bilirubin, LDH, and prothrombin time (PT), are significantly elevated in COVID-19 patients admitted to ICU than in non-ICU patients. Liver failure has also been observed with other organ failures in nonsurvivors of COVID-19 infection.

GI tract involvement

Emerging data suggests involvement of gastrointestinal tract in COVID-19 infection. Patients have presented with symptoms such as loss of appetite,

Nausea and vomiting, Diarrhoea and abdominal pain. The intestinal damage caused by SARS-CoV-2 infection has been verified by autopsy and biopsy.

Septic Shock

Secondary infections together with the Covid infection, may result in sepsis and septic shock. Sepsis may be a result of dysregulated host response to infection. Viral sepsis and cytokine storm are major component in the pathogenesis of COVID-19 and significantly contribute to the COVID-19-related mortality.

Disseminated Intravascular Coagulation and blood clots

Disseminated intravascular coagulation (DIC) is a complication associated with COVID-19 which leads to formation of abnormal blood clots further causing internal bleeding or organ failure. Some patients present with deep vein thrombosis or DVT, pulmonary embolism, or clots in arteries but not with DIC. Some researchers have suggested the occurrence of a new clotting condition, COVID-19-associated coagulopathy (CAC). It's marked by different protein levels in your blood than the ones caused by DIC.

Multisystem Inflammatory Syndrome in Children

Some children and teens are hospitalized with a condition called multisystem inflammatory syndrome in children. Symptoms include fever, belly pain, vomiting, diarrhea, rash, headache, and confusion. They're similar to those of toxic shock syndrome or Kawasaki disease, which causes inflamed blood vessels in children. Clinicians suggest its link to COVID-19 infection

Rhabdomyolysis

An extremely rare complication associated with COVID-19. In rhabdomyolysis, muscles break down and tissue dies as a result, myoglobin floods the bloodstream. If the blood is not flushed out quickly, this may lead to death.

Neurological Complications:

There is clinical evidence that the SARS-CoV-2 has potential neuropathic properties. Several neurologic-related symptoms have been reported, including headaches, dizziness, seizure, peripheral neuropathy, decreased level of consciousness, acute haemorrhagic necrotizing encephalopathy, agitation and confusion. In some Covid patients, stroke can be a presenting complaint or subsequent complication.

Cardiac Complications

Cases of COVID-19 have resulted in myocarditis, cardiomyopathy, arrhythmias and dilation of coronary and other blood vessels due to vascular inflammation as well as blood clots.For patients with a prior history of cardiovascular disorders and increased risk factors, such as hypertension and diabetes, chances of heart complications significantly rise when infected with COVID-19.

Pregnancy Complications:

Pregnant women with Covid infection have a higher risk of obstetric complications and adverse perinatal outcomes compared to nonpregnant women, possibly due to concomitant changes in the immune response. COVID-19 has also been associated with poorer perinatal outcomes, including spontaneous abortion, maternal death, and preterm birth.

Recurrence of COVID-19 after Recovery

Scientists and clinicians indicate a possibility of relapse of COVID-19 infection in recovered patients with a weak immune system. There have been cases in Italy, China and India who have reported relapse of infection. Antibody responses occur in those who have been infected. However, for how long these antibodies will protect the individual is yet to be established. All patients are advised a quarantine of 14 days but there is no clear definition of the infectiousness timing and duration of viral shedding. The possibility of a reactivation of COVID-19 poses a major public health concern.

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Section B

Preventive measures

06 Preventive Measures For Healthy People

COVID-19 was declared as a Public Health Emergency of International Concern in January 2020 and a global pandemic in March 2020. Since then the number of cases being infected are exponentially increasing and so is the mortality. Over 3.3 million people have been infected all over the world.

Who is at risk?

- Both men and women are at equal risk of COVID-19 infection and have the same prevalence but studies have shown that men with COVID-19 are more at risk for worse outcomes independent of age.
- People over age of 60 years
- Individuals with underlying co-morbidities such as diabetes, hypertension, heart diseases, cancer, pre-existing respiratory conditions are at a higher risk and they also progress faster to more severe forms of COVID-19 and develop complications.
- Children of all ages are also susceptible to COVID-19. Children with underlying conditions such as congenital heart, lung and airway disease, chronic heart and kidney disease, malnutrition, hereditary metabolic diseases, immunodeficiency disease, tumor, etc. are likely to become severe cases.
- Family members of COVID-19 patients are at high risk getting infected themselves

- Healthcare providers and frontline workers
- People who have travelled to or from other countries.

Mode of transmission of virus:

The virus often spreads through close contact from person who has symptoms. However, it is also possible to pass it on through people who do not show any symptoms of infection. This is called asymptomatic spread. Virus may be transmitted in the following ways:

1. Droplets/aerosols: Droplets/aerosols from the nose or mouth of an infected person when they cough, sneeze or talk act as the medium for spread of disease. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.One can get the infection by being in close contact.

Aerosols are droplets containing pathogens (viruses or bacteria) that are suspended in the air for a long period of time. They are generated during breathing, talking, coughing and sneezing and have the potential for long-distance disease transmission.

2. Airborne transmission: Recently, it was reported that the virus can survive in the air for up to 3 hours.

3. Fomite transmission: Droplets/aerosols secreted by infected patients can contaminate surfaces and objects (fomites). COVID-19 virus survives in aerosols for 3 hours whereas it is found to survive on plastic and steel surfaces for upto 72 hours and on cardboard surfaces for 24 hours. As a result, virus transmission can occur indirectly by touching contaminated surfaces

4. Fecal-oral and urinary transmission: Recently, SARS-CoV-2 was isolated from the feces and urine of patients with COVID-19. Evidence indicates that the virus can survive in the digestive tract and the urethra, and suggest that SARS-CoV-2 could be transmitted via the fecal-oral or urinary route.

5. Mother-to-child transmission: There is a new found possibility that a mother infected with COVID-19 can give birth to a child who is also infected. Transmission of the virus can take place before the birth, in the mother's womb through the placenta, or during delivery from an infected pregnant mother. However, there appears to be a minimal risk of fetal infection via known routes of vertical transmission.

Things to do to prevent spread of virus

There is extensive research being conducted worldwide to establish a definitive treatment. However, the only way to control the pandemic is to prevent the spread of this virus. It is important for every individual to take the right preventive measures to not get sick or infect others and prevent community infection. It is a known saying that "Prevention is better than cure" but if there is no definitive cure available,prevention is the only effective cure.

General Precautions

General precautions to be taken:

- Wash hands frequently and thoroughly with soap and water for at least 20 seconds or use alcohol based hand rub with at least 60% alcohol to clean hands especially after direct contact with people.
- Wear a mask in public places.
- Maintain at least 6 feet distance between themselves and others.
- Be in a well ventilated place and not in an airconditioned room as it increases the chances of infection.
- Avoid crowded places as the possibility of coming in close contact with an infected person is high in crowded places where distance of 6 feet cannot be maintained.
- Avoid touching eyes, nose and mouth. Hands may get contaminated and can transfer the virus through eyes, nose or mouth and lead to infection.
- Follow good respiratory hygiene by covering mouth and nose with bent elbow or tissue while coughing or sneezing. Used tissue should be disposed immediately followed by hand hygiene.
- Avoid sharing personal items such as drinking glasses, dishes, and towels with other family members.
- To stay at home unless there is essential work. All non-essential travel should be avoided
- Seek medical attention at the earliest if there are any symptoms such as cough, headache, fever and self isolate.

Cleaning and Disinfection:

- All items/ groceries should be sanitized using disinfectant spray or soap water before use
- For couriers, contactless delivery should be opted whenever possible. Non-perishable items should be kept out/ in a basket at the door for 24 hours. The outer packaging such as delivery bags, boxes and containers should be sanitized and disposed off. Hands should be washed thoroughly after handling these items.
- Vegetables should be washed with warm water before use
- Immediate bath with warm water should be taken after coming home from public places.
- Used clothes, bed linens, and bath and hand towels should be cleaned using regular laundry soap and water or machine washed at 60–90°C with common laundry detergent.
- High touch surfaces such as phones, remote controls, door knobs, switches, handles, etc should be cleaned and disinfected daily. For surfaces that cannot be cleaned with bleach, 70% ethanol can be used.
- Toilets and bathrooms should be cleaned and disinfected with a diluted bleach solution (one part bleach to 9 parts water to make a 0.5% sodium hypochlorite solution).
- Disposable gloves should be used when cleaning or handling surfaces, clothing, or linen soiled with body fluids.
- All used disposable contaminated items should be placed in a lined container before disposing of them with other household waste.
- Cleaning and disinfecting medium such as sanitizers, alcohols, bleach solutions need to be used cautiously if not then they may cause even more damage. For example, bleach solution when mixed with vinegar or ammonia or exposed to heat may generate chlorine and chloramine gases which result in severe lung damage on inhalation. Ingestion of sanitizers or cleaning solutions may lead to alcohol toxicity, irritation of mucous membrane, gastrointestinal .

Precautions to be taken while travelling to work:

- Wear a mask while travelling
- Avoid public transport.
- If using public transport, maintain a distance of 6 feet. Sitting or standing within 6 feet of others may increase risk of getting COVID-19
- Maintain respiratory hygiene and encourage fellow travellers to do the same
- Sanitize hands regularly. Wash hands immediately after reaching destination.

Precautions to be taken at workplace:

- Work from home should be encouraged where possible.
- Hygiene should be maintained at the workplace
- Surfaces such as keyboards,chairs, tables, desk, telephones should be wiped and disinfected regularly
- Washrooms should be cleaned and disinfected regularly using disinfectant containing a diluted bleach solution.
- Disposable gloves should be used when cleaning or disinfecting surfaces.
- Employees should wash hands frequently
- Social distance should be maintained.
- Respiratory etiquettes should be encouraged like covering mouth and nose while coughing/ sneezing.
- Working stations should not be close to each other.
- Use of Air Conditioners should not be encouraged.
- Temperature and oxygen saturation (SpO2) measurements should be taken for each employee daily.

Medicines/ Supplements:

- Many studies have evaluated the benefits of using nutritional supplements and herbal concoctions for stimulating immunity.
- Multivitamins consisting of Zinc, Magnesium, Vitamin C, D & E, omega-3 fatty acid, Selenium, N-acetylcysteine and other micronutrients help in improving immune function of the body.
- Use of alternative medicines such as ayurvedic herbs and homeopathy medicines may also help in immunity boosting
- Daily steam inhalation and salt water gargles are also helpful preventive practices.
- Drink herbal tea / decoction (Kadha) made from Tulsi (Basil), Dalchini (Cinnamon), Black pepper, Dry Ginger and Munakka once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.
- Intake of Golden Milk- Half tea spoon Haldi (turmeric) powder in 150 ml hot milk -once or twice a day.

Dietary Advice:

- Diet plays an important role in boosting immunity and overall health.
- Eating a healthy, low carbohydrate diet, will control high blood sugar and blood pressure.
- Protein-rich diet helps in muscle building.
- Regular consumption of vegetables and fruits rich in Beta carotene, Ascorbic acid and other essential vitamins boost immunity. Certain foods like mushrooms, tomato, bell pepper and green vegetables like broccoli, spinach are also good options to build resilience in the body against infections.
- Ginger, gooseberries (amla) and turmeric are natural dietary immune boosting supplements
- Anti inflammatory and anti-oxidant rich diet should be consumed

Lifestyle Changes

- Ministry of AYUSH has recommended daily practice of Yogasana, Pranayama and meditation for at least 30 minutes.

- Good quality sleep for 7-8 hrs along with being physically active helps in building immunity against the virus.
- Exercises to improve mental health should be practiced

When to consult a physician?

- Immediate medical attention should be seeked incase of common symptoms such as fever, cough, sore throat, shortness of breath, loss of taste and smell, extreme fatigue etc.
- If SpO2 <96
- People with mild symptoms who are otherwise healthy should manage their symptoms at home with doctor's advise and under medical supervision.
- On average it takes 5–6 days from when someone is infected with the virus for symptoms to show, however it can take up to 14 days.

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Sample Prescription for Immune Boosting:

Rx

1. Tab Vit C 1 gm po 1-0-1 x 15 days
2. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
3. Tab Zinc 50mg po 0-1-0 x 15 days
4. Tab Magnesium 500mg po 0-0-1 x 15 days
5. Tab Selenium 100 mcg po 1-0-0 x 15 days
6. Tab Multivitamin po 0-1-0 x 15 days
7. Syp Vit D3 60K po once a week for 4 weeks
8. Steam inhalation 4 times a day
9. Ayush Kadha daily for 7 days
10. Frequent intake of warm water for drinking all day. Avoid cold water and cold food.
11. Warm salt water gargle daily
12. Turmeric water alternate day

07 Preventive Measures For Covid Contacts

A contact is a healthy individual who has been in close association with an infected person or contaminated environment and therefore is at a higher risk of getting infected. Preventive measures are the current strategy to limit the spread of cases. Early screening, diagnosis, isolation, and treatment are necessary to prevent further spread. Preventive strategies should focus on the isolation of patients and careful infection control.

For the purpose of implementing quarantine, a contact should be involved in any of the following from 2 days before and up to 14 days after the onset of symptoms in the patient

- A contact means being closer than 6 feet for 15 minutes or more with an infected person.
- A person living in the same household or sharing a workplace, classroom or being at the same gathering for any amount of time as a COVID-19 positive patient.
- A person having had direct physical contact with a COVID-19 patient or with infectious secretions without personal protective equipment (PPE) or with a possible breach of PPE
- A person who has travelled together in close proximity with an infected person.

Things to be done in case of contact with a COVID-19 patient

- According to WHO recommendations, contacts of patients with laboratory-confirmed COVID-19 should be quarantined for 14 days from the last time they were exposed to the patient.

- Quarantine at home in a well ventilated room preferably with an attached/separate toilet for 14 days. Use a separate bathroom. It is one of the most effective ways of controlling communicable disease outbreaks such as COVID-19. Quarantine is the restriction of activities of or the separation of persons who are not ill but who may have been exposed to Covid virus. The main objective is monitoring of symptoms and ensuring early detection of infection.

- Watch for symptoms such as cough, shortness of breath or difficulty breathing, fever, chills, fatigue, muscle pain or body aches, headache, sore throat, loss of taste or smell, congestion or runny nose, nausea or vomiting, or diarrhea

- SpO2 should be monitored periodically and should be > 96%

- Stay at least 6 feet away from others at home at all times especially elderly people, people with co-morbidities, pregnant women, children.

- Wear a mask if surrounded by other people.

- Don't share household items such as dishes, glasses, spoons, cups, towels, bedding, etc.

- Maintain Hand hygiene

- Maintain respiratory etiquette

- In case of any symptoms get tested for Covid

- Should take a prophylactic dose of HCQ under medical supervision. However, this should not instill false security. The contact should continue being in home quarantine while on prophylactic dose of HCQ and follow all the above precautionary measures.

- Dosage of HCQ: 400 mg twice a day on Day 1 followed by 400 mg once weekly for 3 weeks alongwith meals

- Active monitoring of people who are quarantined is one of the important

points for controlling the epidemic in the society. For Indian Citizens, Aarogya setu application should be downloaded and regularly updated with required information

- High risk contacts should be tested for COVID-19

Environmental sanitation

- Frequently touched surfaces in the quarantined person's room such as bed frames, tables etc should be cleaned and sanitized regularly with 1%Sodium Hypochlorite Solution.
- Household items like utensils should be washed thoroughly after use
- Clothes and other linen used by the person should be washed separately using common household detergent and dried.
- Toilet surfaces should be clean and disinfected daily with regular household bleach solution/phenolic disinfectants.

Things to be done by Family Physician

- Take detailed contact history.
- Counsel the family and the patients about signs and symptoms to watch out for.
- Monitor fever and oxygen saturation
- Prescribe prophylaxis treatment such as HCQ, multivitamins, etc
- If required, qRT PCR test for COVID-19 should be advised
- If the patient has high fever, low saturation patient should be hospitalised immediately

Medical Management:

- As per the Ministry of Health and Family Welfare, India all close contacts should be prescribed Hydroxychloroquine keeping in mind the contraindications of HCQ. Dosage: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals
- HCQ should be taken under strict medical supervision.

- HCQ should not be prescribed to children below 15 years and adults above 50 years with heart conditions, retinopathy, etc.
- HCQ is advised for its virological response and immunosuppressive properties which may help in managing the cytokine storm which is often seen in COVID-19 infection.
- Prescribe multivitamins for immunity boost
- Healthy diet, warm water, herbal teas and concoctions (Kadha) made from Tulsi (Basil), Dalchini (Cinnamon), Black pepper, Dry Ginger and Munakka once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.
- Salt water gargle and steam inhalation 4 times a day should be advised
- Physical activity and yoga for 30 minutes daily is advised
- 7-8 hours of sleep and exercises for mental health management such as meditation, journalling, etc should be practiced

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Sample Prescription

Rx

1. Tab HCQ 400 mg po 1-0-1 on Day 1.Followed by 400 mg once a week x 3 weeks (Take with Meals) (Not for cardiac abnormalities) *
   *if patient has ECG/ cardiac abnormalities not to give HCQ
2. Tab Doxycycline 100 mg po 1-0-1 x 7 days
3. Tab Ivermectin 12 mg po 1-0-0 x 3 days
4. Tab Vit C 1 gm po 1-0-1 x 15 days
5. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
6. Tab Zinc 50mg po 0-1-0 x 15 days
7. Tab Magnesium 500mg po 0-1-0 x 15 days
8. Tab Selenium 100 mcg po 0-1-0 x 15 days
9. Tab Multivitamin po 0-1-0 x 15 days
10. Syp Vit D3 60K po once a week x 4 weeks
11. Cough syrup SOS for cough
12. Tab Paracetamol 500 mg SOS for fever
13. Steam inhalation 4 times a day
14. Ayush Kadha daily for 7 days
15. Frequent intake of warm water for drinking all day. Avoid cold water and cold food.
16. Warm salt water gargle daily 4 times
17. Turmeric water alternate day

08 Preventive Measures For Healthcare Workers

Healthcare workers are at an increased risk of acquiring COVID-19 infection. They could be exposed to a number of infected patients, contacts and colleagues. Improper use of personal protective equipment (PPE), suboptimal adherence to IPC measures, and having a family member with COVID-19 can increase their risk of infection.

Lower risk	Medium risk	High Risk	Very High risk
Administrative staff who do not work in public areas of healthcare facilities.	Healthcare workers who work with general public who are not known to have COVID-19 or in public areas of the healthcare facilities	Health care workers who provide direct care for suspected or confirmed COVID-19 patients.	Performing aerosol generating procedures such as intubation, dental procedures, specimen collection of confirmed or suspected COVID-19

One of the biggest risks to any health-care system is a high rate of COVID-19 infection among healthcare workers and consequent lack of skilled staff to ensure optimum functioning of the hospitals/ healthcare systems. To avoid the breakdown of health care system, it is important for the health care workers to take utmost care and follow preventive measures to be safe and not acquire infection.

Precautions to be taken by hospital set up for safety of their healthcare workers:

- Hospitals managing confirmed or suspected Covid patients Infection Prevention and Control (IPC) activities should be implemented
- Regular extensive training programs for use of PPE, isolation, cleaning and disinfection should be organized for the healthcare workers.
- Regular thermal screening of all hospital staff should be done.
- All healthcare workers managing COVID-19 cases should be provided with prophylaxis under medical supervision.
- Pregnant/lactating mothers and immuno-compromised healthcare workers should not be allowed to work in Covid patient areas
- Environmental hygiene should be maintained in the hospitals.
- Influx of patients should be regulated
- Different areas/zones should be allotted for different purposes. Staff responsible for infected patient care should not be allowed in the areas where there is no patient exposure.
- Separate triage areas should be allotted in hospitals to identify patients likely to be infected or with confirmed diagnosis of COVID-19

Precautions to be taken by Healthcare workers

- Healthcare workers should use appropriate PPEs at all times while on duty according to their risk profiles/ area of work.
- All healthcare workers should undergo training on Infection Prevention and Control
- They should be aware of common signs and symptoms of COVID-19, should self-monitor their health and promptly report presence of symptoms.
- Should frequently wash hands or use alcohol based hand rubs to sanitize hands
- Should follow respiratory etiquettes

- On leaving the patient care units, healthcare workers must follow social distancing and wear mask.
- Should promptly report breach of PPE. A buddy system should be followed where in another staff member shares responsibility of safety and well-being of their partner in the context of (i) Appropriately donning and doffing of PPEs, (ii) maintaining hand hygiene and (iii) taking requisite steps on observing breach of PPEs
- If there is a breach of PPE amongst healthcare workers with high risk exposure, they should be quarantined for 14 days, monitored for symptoms and managed as per protocol and should be tested for COVID-19.
- In case of exposure/ breach of PPE of Low risk contacts, they should continue working and self monitor symptoms.
- At home, the healthcare workers should maintain social distance from their family members.
- If they work with Covid positive patients, they should live in an isolated well ventilated room preferably with a separate bathroom.
- They should use separate personal items such as eating utensils, bedsheets, towels and napkins.

Rational use of PPE for healthcare workers:

- Ministry of Health and Family Welfare, India has recommended rational use of PPE for healthcare workers based on treatment areas of the hospital.
- In mild risk areas such as help desks, pharmacy counters, etc a triple layer medical mask along with latex examination gloves are recommended.
- In moderate risk areas such as Triage, doctor's chamber, Pre-anesthetic check up clinic, Chamber of Dental/ENT/ ophthalmology doctors, sanitary staff, etc, N-95 mask, goggles, latex examination gloves and a face shield is recommended.
- In high risk areas such as ICU/critical care a complete PPE is recommended.

If any healthcare worker shows signs and symptoms suggestive of COVID-19:

- He/she should be isolated immediately.
- In case of mild/very mild/pre-symptomatic case, home isolation should be advised.
- If home isolation is not feasible, these cases should be admitted to a Covid Care Center.
- Moderate cases that require oxygen therapy should be admitted at a Dedicated Covid Health Center.
- Severe cases should be managed in a Dedicated Covid Hospital.

Management for Healthcare workers

- All healthcare workers should be advised 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals
- Multivitamins
- Healthy diet
- Adequate hydration should be maintained. Warm water, herbal teas and concoctions should be taken daily on regular basis
- Salt water gargle and steam inhalation 4 times a day should be advised
- Physical activity and yoga for 30 minutes daily.
- Psychological support is one of the key factors to reduce hardships of healthcare workers working during the pandemic. They experience tremendous physical and mental exhaustion. Most of them are often away from their friends and families to avoid risk of infection. For those managing emergency and the intensive care units, working long hours, over exertion, staff shortages and deficient supplies adds to their emotional and physical stress. Anxiety, depression, insomnia, loneliness, etc experienced by the healthcare workers may take a toll on their overall well being and eventually may impact healthcare services.

Novel approach for prophylaxis in healthcare workers

Medical ozone therapy has been used as a novel approach for prophylaxis in healthcare workers. A study was conducted on healthcare workers at NeuroGen

Brain and Spine Institute, a dedicated covid hospital, wherein 64 received the ozone prophylaxis and 171 did not. The incidence of COVID-19 was significantly lesser in the group that received ozone prophylaxis as compared to those who did not. Benefit was seen irrespective of the risk of exposure. No major adverse events were noted.

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Sample Prescription

Rx

1. Tab HCQ 400 mg po 1-0-1 on day 1 followed by 400 mg once a week for next 7 weeks (take with meal) (Not for cardiac abnormalities) *
2. Tab Vit C 1 gm po 1-0-1 x 15 days
3. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
4. Tab Zinc 50mg po 0-1-0 x 15 days
5. Tab Magnesium 500mg po 0-0-1 x 15 days
6. Tab Selenium 100 mcg po once a day x 15 days
7. Tab Multivitamin po 0-1-0 x 15 days
8. Syp Vit D3 60K po once a week for 4 weeks
9. Steam inhalation 4 times a day
10. Ayush Kadha daily for 7 days
11. Frequent intake of warm water for drinking all day. Avoid cold water and cold food.
12. Warm salt water gargle daily
13. Turmeric water alternate day

Section C

Management of Covid Patients

09 Management of Suspected Covid Patients

A suspected Covid patient is the one who may meet the epidemiological and clinical criteria specific to COVID-19. Family physicians are the first to be contacted if an individual notices any common symptoms of COVID-19. They see a large number of patients with viral fever. However, COVID-19 is a new disease and its epidemiological pattern is still uncertain. It is also difficult to differentiate COVID-19 solely on the basis of its symptoms. COVID-19 should not be mistaken with normal flu syndrome. Hence, the role of a family physician is of utmost importance in distinguishing COVID-19 from other flus and making timely decisions regarding management of the suspected individual. Early detection of COVID-19 can prevent patients from developing severe irreversible symptoms for which there may be a requirement of intensive care or highly invasive procedures such as intubation and mechanical ventilation, which currently results in a high mortality rate. In order to break the chain of transmission, it is important to isolate every suspected or confirmed case, provide appropriate treatment and trace their contacts at the earliest.

Ministry of Health and Family Welfare, Govt. of India has defined a suspected case as

A. 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

B. 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

C. A patient with severe acute respiratory illness (fever and at least one sign/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.

Epidemiological Criteria to be considered by the Family Physician :

14 days prior to illness onset if the patient has experienced the following:

- Close contact with a confirmed or probable case
- A history of travel to or residence in a country/area or territory reporting local transmission
- Healthcare, aged or residential care workers and staff with direct patient contact
- People who have lived in or travelled through a COVID-19 hotspot

Clinical Criteria to be considered by the Family Physician :

- There may be asymptomatic carriers or individuals with symptoms such as fever and at least one symptom of respiratory disease (e.g., cough, shortness of breath)
- Typical presentation of COVID-19 is intermittent fever and dry cough, shortness of breath on 4th or 5th day. Continuation of fever beyond ten days is unusual. However, very high-grade fever which is associated with cytokine storm, continues beyond ten days. The course of illness is 15 to 20 days or even longer from the day of onset of symptoms.
- The patients may rapidly deteriorate and develop Acute Respiratory Distress Syndrome (ARDS) within a short span of time; further requiring intensive care units and ventilator support.
- Other reported symptoms of COVID-19 include loss of taste, loss of smell, fatigue, runny nose, muscle pain, joint pain, diarrhoea, nausea/vomiting and loss of appetite.

- "Silent hypoxia" is also one of the conditions often noticed in COVID-19 patients. In normal pneumonia, patients experience chest pain and significant breathing difficulties. But, in COVID-19 pneumonia, the hypoxia .i.e oxygen deprivation is difficult to detect as the patients do not experience any noticeable breathing difficulties. By the time patients experience breathing difficulty, their conditions have already deteriorated significantly. Thus, detection of silent hypoxia in COVID-19 patients before they develop shortness of breath is critical for preventing the pneumonia from progressing to a severe level.

- Clinical judgement should be used to determine if individuals with sudden and unexplained onset of one or more of these other symptoms should be considered suspect cases.

- A case for whom testing for COVID-19 is inconclusive.

- Neurological manifestations of COVID-19 are not uncommon. These include myalgia, headache, altered sensorium, hyposmia, and hypogeusia. Ischemic stroke, intracerebral hemorrhage, encephalo-myelitis, and acute myelitis, Guillain-Barré syndrome, Bell's palsy, and rhabdomyolysis have also been reported

Role of a Family Physician

- Take detailed exposure and clinical history.

- Monitor fever, vitals and oxygen saturation levels (SpO2) for early detection of pneumonia.

- Order laboratory tests such as CBC, ESR, CRP, D-Dimer, LDH, etc, Chest X-ray, qRT-PCR/Rapid Antigen Test

- Order High Resolution CT scan for accurate diagnosis and and to know the extent of lung damage, if any

- If the qRT-PCR results are positive, the patient is COVID-19 positive regardless of other symptoms.

- If the qRT-PCR results are negative but the HRCT suggests infection and the patient shows clinical symptoms or has a history of exposure, the patient can be considered Covid positive.CT findings have been reported to vary at different stages of the disease. An appearance consisting primarily of ground-

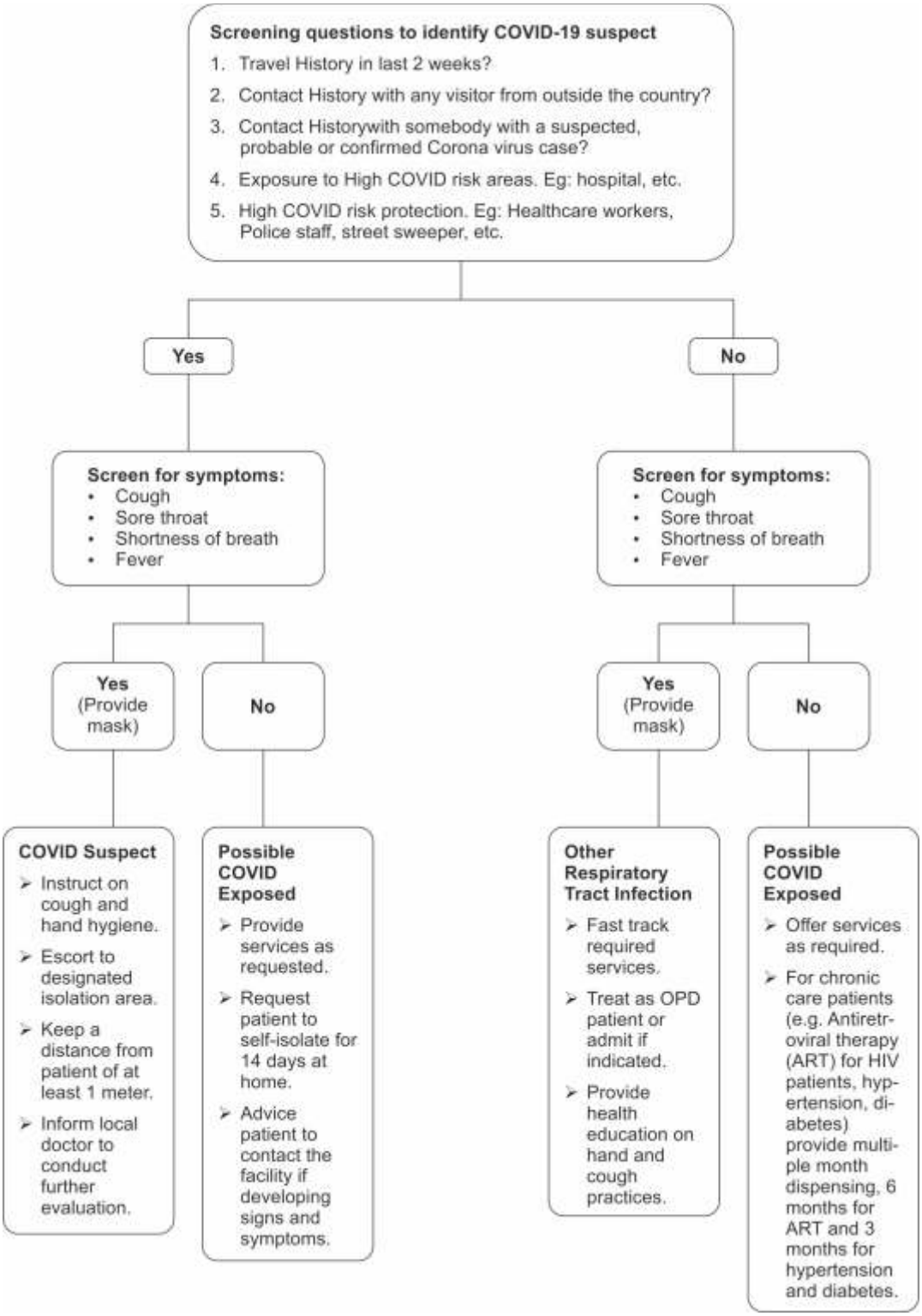

Table 1- COVID Suspect

glass opacification (GGO) with comparatively less consolidation is reported to be the principal manifestation on CT images obtained before onset of symptoms and for up to 1 week after symptom onset. GGO decreased in the more advanced stages of COVID-19 pneumonia, but consolidation or mixed consolidation and GGO increased, and reticular patterns are seen in the later stages (more than 1 week after symptom onset)

- Patients with mild symptoms, history of exposure, but negative qRT-PCR and CT findings not typical of COVID-19 infection, may not be infected with Covid but should be advised isolation.

- All suspected patients should be advised quarantine, routine precautionary measures such as hand hygiene, respiratory etiquette, wearing a mask, etc until test results are available

- Patients should be counselled about signs and symptoms of complications that require urgent care.

- Patients with risk factors for severe illness should be monitored closely, given the possible risk of deterioration. If they develop any worsening symptoms (such as light headedness, difficulty breathing, chest pain, dehydration, etc.), they should be immediately admitted to a Dedicated Covid Health Centre or Dedicated Covid Hospital.

- Suspected children should be monitored for difficulty in breathing/fast or shallow breathing (for infants: grunting, inability to breastfeed), blue lips or face, chest pain or pressure, new confusion, inability to awaken/not interacting when awake, inability to drink or keep down any liquids.

- Initial medical care should be prescribed based on the symptoms such as antipyretic (Paracetamol) for fever and pain, adequate diet and appropriate rehydration till diagnosis is confirmed.

- Immune boosting supplements, healthy diet, herbal teas/ decoction made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, should be advised.

- Frequent intake of warm water for drinking all day should be advised. Cold water and cold food should be avoided.

- Warm salt water gargle daily should be advised

- Steam inhalation 4 times a day should be advised
- Medicine to be given with caution
- Patients who are clinically assigned as moderate or severe should be advised hospitalization

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Sample Prescription

Rx

1. Tab HCQ 400 mg po 1-0-1 on Day 1. Followed by 200mg 1-0-1 x 4 days. (Take with meal) (Not for cardiac abnormalities) *
2. Tab Pantoprazole and Domperidone D 40 mg po 1-0-1 x 5 days
3. Tab Vit C 1 gm po 1-0-1 x 15 days
4. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
5. Tab Zinc 50mg po 0-1-0 x 15 days
6. Tab Magnesium 500mg po 0-1-0 x 15 days
7. Tab Selenium 100 mcg po 0-1-0 x 15 days
8. Tab Multivitamin po 0-1-0 x 15 days
9. Syp Vit D3 60K po 0-1-0 x 3 days. Then once a week for 4 weeks
10. Cough syrup po 1-1-1 x 7 days
11. Tab Paracetamol 500mg po 1-1-1 if having fever
12. Steam inhalation 4 times a day
13. Ayush Kadha daily for 7 days

*if patient has ECG/ cardiac abnormalities give
Tab Doxycycline 100 mg po 1-0-1 x 7 days
Tab Ivermectin 12 mg po 1-0-0 x 3 days

** If patient has cough Add
#Tab Azithromycin 500 mg po 1-0-0 x 5 days OR
Tab Amoxicillin/ Clavulanate 625 mg po 1-0-1 x 7 days

#Note: when combined with HCQ there is risk of QT prolongation so, this combination is to be avoided in patients above 60 years and with cardiac history.

10 Management of Covid Positive Patients In Home Isolation

Home isolation is advised for individuals who are suspected or have confirmed diagnosis of COVID-19 and are very mild/pre-symptomatic/asymptomatic as per a physician. Ideally, these patients do not need to be hospitalized, and can be managed at home

Eligibility for Home Isolation

- Patient shall be clinically assigned as an asymptomatic/mild case by the treating medical officer/ physician.
- Should have requisite facility at home for self-isolation and also for quarantine of family contacts. A separate, well-ventilated room with a separate toilet for the person in isolation should be available.
- A caregiver should be available to provide care 24×7.
- Mild fever < 38° C(< 100.4° F)
- Oxygen saturation should be > 95%
- Age shall be less than 60 years
- Comorbidities such as hypertension, diabetes mellitus, obesity, thyroid disease should be well-managed and under good clinical control as assessed by the medical officer/physician
- The patient should not have comorbid conditions like kidney diseases including need for dialysis, heart diseases, stroke, Tuberculosis, cancer, HIV.

Should not be immune-compromised and/or on steroids and immune-suppressants, etc.

- Home isolation shall not be applicable for pregnant women four weeks before the expected date of delivery.
- The patient should give a signed undertaking on self-isolation and follow the government guidelines of home isolation.
- Patient should agree to monitor their own health and regularly inform their health status to the physician and District Surveillance Officer (DSO) for further follow up by the surveillance teams.
- The person shall have a pulse oximeter, digital thermometer and personal protective equipment (facemasks, gloves) to be used during home isolation.
- Home isolation should be with the knowledge of the family members, neighbours, treating physician and the local health authorities.

If the person is not eligible for home isolation or the house is not suitable for it, then isolation at a facility (COVID Care Centre/ Dedicated COVID Healthcare Centre/ Designated COVID Hospital) is recommended.

Home isolation for Pediatric patients

- For children without any clinical symptoms and mild infection, home isolation for 2 weeks is recommended.
- Symptoms should be medically managed.

Precautions to be taken by the patient in home isolation (Figure 1)

Figure 1, 2- wear a mask, cover while sneezing

- Patients should wear a medical face mask/ N-95 face mask at all times. The masks should be discarded after eight hours of use, or earlier if it becomes wet or visibly soiled. (after disinfecting it with 1% sodium hypochlorite solution)

- Patients must stay in the identified room only, and maintain a physical distance of 6 feet from other people in the home, especially the elderly and those with comorbid conditions like hypertension, cardiovascular disease, renal disease, etc.

- The patient should take rest and drink a lot of fluids to maintain adequate hydration.

- Follow respiratory etiquette at all times

- Wash hands often with soap and water for at least 40 seconds or clean them with an alcohol-based sanitiser.

- Not to share personal items like utensils, towels, etc., with other family members and should be stored separately.

- Surfaces in the room that are touched often (table-tops, doorknobs, handles, etc.) should be cleaned regularly with 7% Lysol or 1% sodium hypochlorite solution.

- Bathroom and toilet surfaces should be cleaned and disinfected at least once daily. Regular household soap or detergent should be used first for cleaning, followed by 1% sodium hypochlorite solution.

- Patients should strictly follow the physician's instructions and medication advice.

When to seek further medical advice

The patient should immediately seek further medical advice if the following symptoms and signs develop;

- Difficulty in breathing

- Oxygen saturation < / = 94% using a fingertip pulse oximeter

- Persistent fever of >38° C (100.4° F) for more than 24 hours

- Persistent pain/ pressure in the chest

- Mental confusion
- Slurred speech/seizures
- Weakness or numbness in any limb or of face
- Developing bluish discolouration of lips/face
- Any other symptom the person considers serious as advised by treating physician

Precautions to be taken by caregivers

Fig. 3,4 - Isolate, wash hands

- The caregiver should wear a medical face mask/ N-95 face mask appropriately when in the same room with the ill person. The front portion of the mask should not be touched or handled during use.
- If the mask gets wet or dirty with secretions, change it immediately. Discard the mask into a separate closed bin after use, and perform hand hygiene afterwards.
- Avoid touching eyes, nose or mouth.
- Hand hygiene should be ensured following contact with the person.
- Hand hygiene should be practised before and after preparing food, before eating, after using the toilet, and whenever hands look dirty. Use soap and water for hand washing for at least 40 seconds. Alcohol-based hand rub can be used if hands are not visibly soiled.
- Disposable paper towels should be used to dry hands.

- Direct contact with body fluids of the patient, particularly oral or respiratory secretions should be avoided.
- Disposable gloves should be used while handling the patient. Hand hygiene should be performed before and after removing gloves.
- Exposure to potentially contaminated items (e.g. avoid sharing food, utensils, dishes, drinks, used towels or bed linen) should be avoided.
- Food must be provided to the patient in his/her room.
- Utensils and dishes used by the patient should be cleaned with soap/detergent and water, wearing gloves. The utensils and dishes may be re-used for the patient.
- Patient's clothes, bed linen, and bath and hand towels should be washed separately using regular laundry soap and warm water, or machine-washed at 60-90 °C (140-194 °F) with common household detergent, and sun-dried thoroughly.
- Gloves and protective clothing (e.g. plastic aprons) should be used when cleaning surfaces or handling clothing or linen soiled with body fluids. Disposable gloves should be used.
- The caregiver should make sure that the person follows the prescribed treatment.
- The caregiver and all close contacts should monitor their own daily temperature, and report promptly if they develop any symptom suggestive of COVID-19 (fever, cough, cold, sore throat, difficulty in breathing, etc.)
- Instructions to family members of the person in home isolation
- Do not panic. Do not stigmatise.
- Keep the person cheerful and boost their morale
- Ensure that the person is in strict home isolation
- Maintain a physical distance of at least 6 feet
- Visitors should strictly not be allowed until the person has completely recovered and has no symptoms of COVID-19

Medical Management

- Investigations such as Complete blood count, random sugar, HbA1C (if diabetic) and ECG should be advised by the physician.
- Hydroxychloroquine should be prescribed to the patient, caregivers and immediate family members/contacts considering its contraindications.
- Tab Zinc 50mg
- Tab Vitamin C 500mg
- Antitussive cough syrups
- Tab pantoprazole
- Tab paracetamol
- Medications for pre-existing comorbidities.

Diet management:

- Healthy balanced diet is advised.
- Home cooked food with less oil should be consumed
- 8-10 glasses of Warm water, herbal decoctions and teas should be consumed
- Whole grains, beans, lentils and pulses high in protein should be consumed
- Fresh fruits and vegetables after thorough cleaning should be used
- Immune boosting food items such as turmeric, ginger, etc
- Smoking, chewing tobacco and alcohol intake shall be strictly avoided.

Psychological Impact and Mental Health management

- Quarantined people often experience boredom, loneliness, anger, depression, anxiety, denial, despair and insomnia.
- They also experience shame and guilt regarding the aftermath and stigma on their family and close contacts.

- As a continuation of safety behaviours, they may develop obsessive-compulsive disorder (OCD).
- The children who have been quarantined have higher chances to develop PTSD, acute stress disorder, adjustment disorder and grief.
- Along with the patient, the family members and close contacts also face psychological problems such as anxiety, depression, resentment
- It is important to manage these mental health issues of people in home isolation and their families for healthy recovery.
- Professional help is advised such as counselling and psychiatric treatment if required.
- Activities for overall well being are encouraged which include physical exercises such as yoga and stretching, relaxation exercises like breathing, meditation and mindfulness, reading, listening to music, etc

When to release the person from isolation at home

- Patient should end home isolation 17 days after onset of symptoms (or date of sampling, for asymptomatic cases) and no fever for 3 days.
- They shall be released if the following criteria are met:
    - No symptoms
    - No fever (recorded temperature < 37.5°C or <99.5° F)
    - Maintains saturation above 95%
    - Respiratory rate less than 24 per minute
- There is no need for RT-PCR test after home isolation period.
- Patient should be allowed to resume work only after satisfactory completion of home isolation and after a fitness certificate from medical officer/physician.
- After completion of home isolation, the house specially the room in which the patient was isolated should be thoroughly cleaned and disinfected with 7% Lysol or 1% sodium hypochlorite solution.

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Sample Prescription

Rx

1. Tab HCQ 400 mg po 1-0-1 on Day 1. Followed by 200mg 1-0-1 x 4 days. (Take with meal) (Not for cardiac abnormalities) *
   *if patient has ECG/ cardiac abnormalities not to give HCQ
2. Tab Doxycycline 100 mg po 1-0-1 x 7 days
3. Tab Ivermectin 12 mg po 1-0-0 x 3 days
4. Tab Pantoprazole and domperidone 40mg po 1-0-1 x 5 days
5. Tab Vit C 1 gm po 1-0-1 x 15 days
6. Tab Vitamin E and Omega 3 po 0-1-0 x 15 days
7. Tab Zinc 50mg po 0-1-0 x 15 days
8. Tab Magnesium 500mg po 0-1-0 x 15 days
9. Tab Selenium 100 mcg po 0-1-0 x 15 days
10. Tab Multivitamin po 0-1-0 x 15 days
11. Syp Vit D3 60K po once a day x 3 day. Then once a week for 4 weeks
12. Cough syrup po 1-1-1 x 7 days
13. Tab Paracetamol 500mg po 1-1-1 if having fever
14. Steam inhalation 4 times a day
15. Ayush Kadha daily for 7 days

** If patient has cough, add
#Tab Azithromycin 500 mg po 1-0-0 x 5 days OR
Tab Amoxicillin/Clavulanate 625 mg po 1-0-1 x 7 days

#Note: when combined with HCQ there is risk of QT prolongation so, this combination is to be avoided in patients above 60 years and with cardiac history.

11 Hospital Management of Mild and Moderate COVID-19 Patients

Introduction

The COVID-19 outbreak has resulted in a public health emergency of international concern. The disease can result in a range of symptoms from the patient being asymptomatic to developing severe life threatening disease and even death. Characterization of patients by the clinical and co-morbid features is important to effectively manage the disease without excessive burdening of healthcare systems.

Triage

Triage is the first point of contact of the patient with the health care system. The purpose of the triage is to recognize patients with a possible COVID-19 infection and to sort these patients with COVID-19, in order to make decisions regarding the appropriate COVID dedicated facility and care. This ensures that the available resources are optimally utilized. This also ensures that only patients who require oxygen (O2) or moderate and severe cases use up the hospital bed capacity. Assigned dedicated staff, namely physicians or nurses evaluate patients presenting with fever, cough or respiratory symptoms.

A standard triage algorithm or questionnaire is used for identification of patients that are suspected/ probable/ confirmed to have the infection.

A. Suspected case

A patient is said to be COVID-19 suspect case if:

i. He presents with an acute respiratory illness presenting with fever and at least one sign of respiratory disease such as cough or shortness of breath OR,

ii. Presents with any acute respiratory illness and confirms contact with a confirmed or probable case in the previous 14 day before symptom onset OR,

iii. Presents with severe acute respiratory illness, i.e. fever and at least one sign of respiratory disease such as cough or shortness of breath and requires hospitalization and there is no other explanation or alternative diagnosis for the presenting symptoms.

B. Probable case

i. In cases that are suspects but the testing for whom is inconclusive OR,

ii. In cases that are suspects but for some reason testing could not be performed.

C. Confirmed case

A patient is said to be a confirmed case of COVID-19 infection on the basis of laboratory confirmation.

Signs and Symptoms

At the onset of illness, the signs and symptoms are variable. But, over the disease course, the most common symptoms experienced by COVID-19 persons include the following [1-5]

- Fever or chills
- Cough
- Sore throat
- Nasal congestion or rhinorrhea
- Shortness of breath
- Headache
- Fatigue

- Myalgia
- Loss of smell and/or taste
- Diarrhea
- Hemoptysis

Categorization of patients and Hospitalization criteria

Depending on the presenting symptoms, reverse transcription-polymerase chain reaction (RT-PCR) COVID-19 positive patients (or suspected and probable COVID-19 cases) are categorized as mild, moderate or severe to make decisions on hospital admission and treatment options.

A. Mild Illness:

Patients presenting with uncomplicated upper respiratory tract infection with no evidence of hypoxemia or breathlessness are categorized as having mild illness. On examination they have oxygen saturation (SpO2) of ≥ 94% in room air and a respiratory rate (RR) ≤ 24/minute.

B. Moderate Illness:

Patients with signs of pneumonia with no signs of severe disease are categorized as having moderate illness. On examination they have SpO2 of 94%-90% in room air and RR of 24-30/minute.

C. Severe illness:

Patients with signs of severe pneumonia are categorized as having severe illness. On examination, they have SpO2 of < 90% and RR > 30/min.

Cases presenting with fever and/or upper respiratory tract infection such as influenza like illness are considered as mild and very mild and are accommodated in COVID Care Centers. These patients remain as suspects in the Care Centers, preferably in individual rooms and are tested for COVID-19. Those that test positive stay in the center as 'confirmed cases'. Those that test negative are given symptomatic treatment and discharged.

Hospitalization to COVID dedicated hospital is not necessary unless:

- There could be a possibility of deterioration due to presence of

comorbidities such as presence of diabetes mellitus, hypertension and in patients above 65 years of age.

- Patients that are clinically mild with possibility of progression, moderate or severe in their presentation are moved to COVID Health Centre or a dedicated COVID Hospital.

Risk Factors

The major risk for progression to severe disease includes:

- Age more than 60 years (risk increases with increasing age).
- Presence of comorbidities such as diabetes, cardiac disease including hypertension, chronic lung disease, kidney disease and immune-suppression and cancer.

In this chapter we will discuss the management of COVID-19 patients that are hospitalized, namely, those with mild (cases that may progress due to presence of comorbidities) and moderate illness.

Diagnosis

Both oropharyngeal (throat) and nasal swab are collected in sterile tubes with viral transport media (VTM) and transported in cold chain.

Real time or conventional reverse transcription-polymerase chain reaction (RT-PCR) test is recommended as a 'gold standard' test for diagnosis.

If RT-PCR report is not available at time of admission Covid antigen test or Chest HRCT can be done to help in covid diagnosis

Laboratory Investigations on hospital admission

Serological, biochemical and hematological tests that are conducted are given below.

- Qt-PCR analysis for COVID -19 / high resolution computed tomography (HRCT) Chest / Covid antigen
- Complete blood count
- Serum electrolytes test

- Liver function test
- Serum creatinine
- HIV, HCV and HBV test if suspected
- Serum HbA1C if diabetic
- Arterial blood gas (ABG) if there is shortness of breath

Specific Inflammatory Biomarkers:

- C- reactive Protein (CRP), Ferritin, lactate dehydrogenase (LDH), D-dimer
- IL-6 in moderate cases
- ECG (In patients above 50yrs or with comorbidities, daily ECG for 5 days to check QT prolongation from hydroxychloroquine or Azithromycin)
- Chest X-ray
- Vitamin D levels, Vitamin B12, Magnesium levels

Laboratory and Radiographic Findings

A. Laboratory Findings

The following are the commonly seen laboratory findings in hospitalized COVID-19 patients

- Lymphocytopenia, the commonest laboratory finding
- Neutrophilia
- Elevated creatinine
- Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels
- Elevated LDH
- High CRP
- Raised erythrocyte sedimentation rate (ESR)

- High ferritin levels
- Elevated D-dimer
- High Il6
- Elevated Procalcitonin. Its presence may indicate a superimposed bacterial infection.

B. Radiographic Findings

Fig 1 - X-Ray showing Plural Effusion

Fig 2 - CT scan showing Ground Glass Opacities

The most common findings on a chest radiograph include bilateral, peripheral and interstitial infiltrates and/or consolidation though during the early phase of the disease, patients may have unremarkable chest radiographs.

Though not specific, chest computed tomography (CT) scan has a higher sensitivity and can play a role in the management of COVID-19. Even asymptomatic patients have manifested chest CT imaging abnormalities. Combining imaging with clinical features and laboratory findings can facilitate early diagnosis of COVID-19. Ground glass opacification (GGO) is the commonest finding in COVID-19 cases. In the initial stage of the illness, GGO is unilateral and multifocal. This quickly progresses to bilateral, diffuse, multilobar GGO and subsegmental areas of consolidation [10, 11]. In the later stages, crazy paving may be noted. Presence of thickened interlobular and intralobular lines in combination with a GGO pattern is called crazy paving.

To summarize, chest CT changes observed over time, in cases that progress include:

1. Early stage (0-4 days): GGO, partial crazy paving, lower number of lobes involved.

2. Progressive stage (5-8 days): Extension of GGO, increased crazy paving.

3. Peak stage (10-13 days): Consolidation

4. Absorption stage (≥14 days): Gradual resolution. Decrease of GGO and predominance of consolidation.

In addition to visual assessment, the severity of the disease may also be assessed by scoring the percentage involvement of each of the five lobes as follows:

i. < 5% involvement

ii. 5%-25% involvement

iii. 26%-49% involvement

iv. 50%-75% involvement

v. > 75% involvement.

The sum of individual lobar scores gives the total CT score. The range, being '0' (no involvement) to '25' (maximum involvement), where all the five lobes show more than 75% involvement.

Clinical Management and Treatment guidelines for mild and moderate cases

Since there is so far no treatment that's approved, management of the illness is largely supportive as per a patient's needs. The treatment includes supportive management of the presenting symptoms and complications. Oxygen supplementation remains the most crucial intervention. Use of existing drugs that have been approved for other medical conditions has been employed to save time, and resources since the safety, efficacy, mechanism of action and other such data for these drugs are already available.

The treatment protocols are similar through most countries and this includes:

- Hydroxychloroquine, chloroquine phosphate: The 4-aminoquinoline, namely chloroquine is used commonly as an antimalarial and anti-inflammatory drug. One of the earliest studies performed to evaluate the possible effectiveness of pre-approved drugs, was a study that showed the in

vitro activity of chloroquine against SARS-CoV-2 virus [12]. Though the exact mechanism of its antiviral action is not known, it is thought to block receptor binding and thus inhibit viral entry into the cell [13, 14]. Also, it has immune modulating properties which may enhance its antiviral effectiveness. Hydroxychloroquine (HCQ), a derivative of chloroquine, is less toxic. Also, it has shown better anti SARS-CoV-2 activity in vitro [15]. Combination of Azithromycin and HCQ has shown to significantly reduce the viral load in SARS-CoV-2 infections [16]. However, due to risk of QT prolongation, ECG monitoring is recommended when using this drug combination.

- Also HCQ should not be combined with lopinavir / ritonavir or favipiravir or remdesivir

- Corticosteroids: The anti-inflammatory properties of corticosteroids: may reduce the risk of systemic inflammation and exudative fluid in the lung tissue thereby improving hypoxia and minimizing the risk of acute respiratory distress syndrome (ARDS) [17].

- Remdesivir: It is an adenosine analogue and incorporates into the nascent viral RNA chains thereby resulting in premature termination [18]. This drug has shown to shorten hospital stay when used earlier in the illness. In a study including moderate to severe cases of COVID-19 infection, clinical improvement was seen in 36 of the 53 patients following administration [19].

- Favipiravir: It was approved in Japan against influenza pandemic. A study revealed that its use effectively reduced the incidence of fever and cough and showed a high clinical recovery rate in mild and moderate cases of COVID-19 infection [20].

Or

- Lopinavir /ritonavir: Lopinavir which is used in combination with ritonavir, is an antiretroviral protease inhibitor used for the treatment of human immunodeficiency virus (HIV) infection. It was found to be associated with lower adverse clinical outcomes, e.g. ARDS or death [21].Though it has a good safety profile, it may interact adversely with other drugs that are used in critically ill patients.

- Antiparasitic drugs (Ivermectin): This is an FDA approved drug that is used for parasitic infections. It has shown anti SARS-CoV-2 activity in vitro [22]. Used in cases where Hydroxychloroquine/tablet Favipiravir is

contraindicated.

A. Management of cases with mild illness:

As mentioned earlier, patients with mild illness may be managed at COVID Care center or first referral units or community health centers. Patients are followed up daily for temperature, vital parameters and SpO2. Monitoring of patients is essential for any sign or symptom of complication or progression that necessitates immediate referral. In case of worsening symptoms, such as mental confusion/ breathing difficulty/ persistent pain/ pressure in the chest/ bluish discoloration of face/lips/ dehydration/ decrease urine output requires immediate COVID Dedicated Hospital admission. Patients with no breathing difficulty and SpO2 ≥ 94% in room air and respiratory rate (RR) ≤ 24/minute, are assigned a routine isolation bed. Those requiring oxygen support are assigned an oxygen bed.

Mild cases may be given symptomatic treatment including:

i. **Paracetamol** for fever and/or myalgia

ii. **Antitussives** for cough

iii. Ensure adequate nutrition and appropriate hydration

iv. **Tablet hydroxychloroquine (HCQ)** may be considered in the high risk group (mentioned earlier) patients that are admitted to the hospital and can be monitored for QT prolongation.

Dose: 400MG po twice a day on day 1 followed by 200mg twice a day for 4 days.

Or

Favipiravir

Dose of 1800 mg twice daily on day 1 followed by 800 mg twice daily up to day 14.

It might cause prolonged QT interval, which requires monitoring

Or

If HCQ/favipiravir contraindicated,

Tablet Doxycycline

Dose: 100 mg BD for 5 days

and

Tablet Ivermectin

Dose: 12 mg OD for 3 days.

v. **Antibiotics** may be prescribed for superimposed infection.

Tablet Azithromycin

Dose: 500mg once a day for 5 days may be added.

Or

If ECG is abnormal or in presence of cardiac disorder or allergy to Azithromycin,

Tablet Amoxicillin/Clavulanate

Dose: 625mg twice daily (BD) for 5 days

vi. If asthmatic, patients may need **dexamethasone/prednisolone.**

vii. **Supportive therapy**

Certain nutrients have been associated with building immune competence. Vitamin C, D, and Zinc particularly reinforce immunity and hence may be a promising option along with standard care [23].

Vitamin C

Dose: 1 gm po twice a day,

Zinc

Dose: Zinc 50mg po once a day,

Vitamin D3

Dose: 3-6 lac unit IM stat dose.

viii. As a prophylaxis for thromboembolism, aspirin recommended or **Low**

molecular weight heparin

Dose: 0.6 IU SC OD.

in cases where there are progressive symptoms or there is a risk of thromboembolism or D-dimer level is high, Low molecular weight heparin 0.6 IU SC BD.

ix. Rehabilitation

Development and initiation of interdisciplinary (e.g. therapists and psychologists) rehabilitation programs can reduce the complications of the disease per se and/or those resulting from a prolonged hospital stay. Debility;anxiety and fear; neurological; pulmonary; neuromuscular; and cognitive complications are some of the complications that can be reduced if rehabilitation programs are initiated early.

x. Diet

Foods rich in refined carbohydrates, saturated fats, sugars are associated with the development of obesity, type 2 diabetes and also impair an individual's immune defence. Individuals must refrain from eating foods that are high in saturated fats and sugar and instead consume high amounts of fiber, whole grains, unsaturated fats, and antioxidants to boost immune function.

xi. Discharge policy

The patient can be discharged after 10 days of symptom onset and no fever for three days. At the time of discharge, the patient is advised home isolation for another 7 days. No testing required before discharge. Follow up on 14th day by tele-conference

B. Management of cases with moderate illness:

Patients with suspected or confirmed moderate illness (RR≥24 breaths/minute, SpO2 of 90-94% in room air) are admitted to a Dedicated COVID Hospital.

i. Symptomatic treatment is employed, e.g. **paracetamol** for fever and **antitussives** for cough.

ii. Adequate hydration is ensured

iii. **Anti-virals**

a. Tablet Hydroxychloroquine:

Dose: 400MG twice a day on day 1 followed by 200mg twice a day for 4-9 days

OR

Tab Doxycycline 100mg bd for 7 days

and

Tab Ivermectin 12mg od for 3 days

Please note that co-administration of remdesivir or favipiravir with HCQ is to be avoided.

b. Injection remdesivir:

It may be considered in **moderate cases that are on oxygen therapy.**

dose: 200 mg IV on day 1 followed by 100 mg IV daily for another 4 days.

It is a safe drug. The observed minor side effects of the drug include phlebitis, constipation, headache, ecchymosis, nausea and pain in the extremities. Laboratory findings may show transient increase in the liver enzymes, prothrombin time (PT) and blood sugar

It is **contraindicated** in patients with

- severe renal involvement (eGFR <30 ml/ min/ m2 or need for hemodialysis),
- AST/ ALT >5 times upper limit of normal range,
- in pregnant and lactating women
- children < 12 years of age.

c. Favipiravir:

Recommended dose:1800 mg twice daily on day 1 followed by 800 mg twice daily up to day 14.

It might cause prolonged QT interval, which requires monitoring

iv. Anticoagulation

Anticoagulant therapies are recommended in patients that are hospitalized, as a prophylaxis of venous thromboembolism (VTE).

Prophylactic dose of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is recommended.

Dose: Inj Low molecular weight heparin 0.6 IU SC OD daily.

Contraindications include:

- Active bleeding,
- Profound thrombocytopenia,
- end stage renal disease,
- emergency surgery, and
- pregnancy.

v. Oxygen support

Maintaining SpO2 of 92-96% (88-92 % in cases with COPD) is to be targeted.

Depending on the oxygen requirement devices that are used for administering O2 include nasal prongs, masks or masks with breathing or non-rebreathing reservoir bags. In case of use of high flow nasal cannula or simple nasal cannula, N95 mask must be applied over it.

Patients should have a daily 12-lead ECG.

vi. Corticosteroids

Use of corticosteroids may be recommended in patients with underlying asthma or chronic obstructive lung diseases or cytokine storm.

IV methylprednisolone may be considered preferably within 48 hours of admission if inflammatory markers are increased OR if oxygen requirement is increasing and inflammatory markers are increased.

Dose of 0.5 to 1 mg/kg/day for 5 to 7 days followed by tapering of dose

OR

Dexamethasone 0.1 to 0.2 mg/kg for three days is recommended.

The duration needs to be reviewed according to the patient's response to the treatment.

vii. Convalescent plasma from COVID-19 recovered patients

The anti-SARS COV-2 antibody containing plasma of recovered patients can be used to treat the moderate to severely ill COVID-19 patients that are not improving despite use of steroids.

It contains the antibodies developed in natural response to the infection. Convalescent plasma therapy showed beneficial effects in cases of Middle East Respiratory Syndrome (MERS), Ebola and H1N1 influenza [24-26]. Following positive results shown in a trial undertaken on two COVID-19 cases, it has been given approval by Drugs Controller General of India (DCGI) for therapeutic use along with the standard treatment protocol.

Dose: 4-13 ml/kg is recommended (usually 200 ml single dose given slowly over not less than 2 hours).

Prerequisites for initiation of therapy include ABO compatibility and cross matching of the donor plasma, plasma IgG titer above 1:640.

Patient is closely monitored for several hours post transfusion for any transfusion related side effects including allergic reaction.

Use should be avoided in IgA deficiency or immunoglobulin allergy.

viii. Other medications

a. IL-6 inhibitors (Tocililizumab) may be considered in moderate cases with progressively increasing oxygen requirements and/or presence of raised inflammatory markers, namely CRP, Ferritin, IL-6. (IL6 above 100 pg/ml)

Patients should be carefully monitored for secondary infections and neutropenia. Check procalcitonin (pct) levels

Dose: 8mg/kg (max 800 mg at one time) given slowly in 100 ml normal saline over an hour is recommended.

If required, dose can be repeated once after 12-24 hours.

Contraindications include:

- Active infections, namely systemic bacterial/fungal;
- Tuberculosis;
- Active hepatitis; and
- Absolute neutrophil count < 2000/mm3.
- Raised pct levels

b. Few patients with COVID-19 experience secondary, superadded bacterial infection. Empiric antibiotic therapy as per local guidelines may be considered (e.g. meropenem, cefoperazone/sulbactum, ceftriaxone etc).

ix. Management of comorbidities

It is believed that affection of the lungs associated with COVID-19 is mediated by the virus entry through angiotensin-converting enzyme 2 (ACE-2) receptors. Since ACE inhibitors or angiotensin blockers used to treat cardiac diseases, hypertension or diabetes upregulate increased ACE-2 receptor expression; such patients may be at a higher risk of severe COVID-19 infection [27]. Changing to an alternative treatment regimen for these patients may be considered.

x. Monitor

Close monitoring of patients with moderate COVID-19 is required for signs or symptoms of disease progression. Particular attention given to:

i. Increased work of breathing (use of accessory muscles)

ii.Hemodynamic instability

iii.Increase in oxygen requirement

iv. Follow up CRP, D-dimer & Ferritin every 48-72 hourly (if available); CBC with differential count, ALC, renal function test/liver function test daily.

xi. Rehabilitation (by therapists and psychologists) to avoid or reduce cognitive, neuromuscular, respiratory, neurological complications.

xii. Supportive therapy

Certain nutrients have been associated with building immune competence. Vitamin C, D, and Zinc particularly reinforce immunity and hence may be a promising option along with standard care.

- Inj Vit C 1.5 gm IV twice a day for 7 days,
- Tab Zinc 25 mg-50mg po once a day,
- Inj vit D3 3-6 lac unit IM stat dose.
- Inj Multivitamin IV once a day
- Tablet N Acetylcysteine TDS if patients have cough.

xiii. Diet

As described earlier. Consume high amounts of fiber, whole grains, unsaturated fats, and antioxidants to boost immune function.

xiv. Discharge Criteria

Moderate cases with no fever (without antipyretics) and maintenance of SpO2 > 95% for 4 days without oxygen support can be discharged after 10 days of symptom onset. In cases with resolution of breathlessness and no O2 requirement.

HOWEVER,

If a patient on O2 whose fever does not resolve within 3 days and the requirement of O2 continues, such patients may be discharged only after resolution of clinical symptoms and ability to maintain SpO2 >95% without support for 3 consecutive days.

At the time of discharge, the patient is advised home isolation for another 7 days. No testing required before discharge.

RED FLAG SIGNS (if developed patient is shifted to an ICU)

i. Neutrophil Lymphocyte ratio more than 3.5

ii. PaO2/FiO2 ratio less than 300

iii. Markedly Raised IL-6 / CRP/ S.Ferritin / D-dimer/LDH/ Triglycerides

iv. SpO2 - less than 90% on oxygen

v. BP < 90/60 mm Hg

vi. Pulse >120 beats/min or < 55 beats/minute

vii. RR > 35/ min

viii. ECG major abnormalities

ix. Deteriorating CBC, LFT, CREATININE

x. Reduced urine output

If any Red flags sign present admit patient to ICU for close monitoring and intensive management as discussed in the next chapter

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Sample Prescription

For Mild Symptomatic covid patient

Rx

1.*Tab HCQ 400MG po twice a day on day 1 followed by 200mg twice a day for 4 days. (to be taken with meals)

Plus

Tab Azithromycin 500mg po once a day for 5 days may be added. (Before giving azithromycin check daily ECG for signs of QT interval prolongation.)

If ECG abnormal or cardiac disorder or allergic to Azithromycin then give

Tab Amoxicillin/ Clavulanate 625mg twice a day for 5 days

Or

If allergic to HCQ or cardiac abnormalities or abnormal ECG give the following

Tab Doxycycline 100 mg po 1-0-1 x 7 days plus

Tab Ivermectin 12 mg po 1-0-0 x 3 days

2.Tab Pantoprazole and Domperidone 40mg po 1 -0- 1 x 5 days

3.Inj LMWH 0.6 iu s.c daily.

4.Tab Vit C 1 gm po 1 -0- 1 x 15 days

5.Vitamin E and Omega 3 po 1-0-0 x 15 days

6.Tab Zinc 50mg po 1-0-0 x 15 days

7.Tab Magnesium 500mg po 1-0-0 x 15 days

8.Tab Selenium 100 mcg po 1-0-0 x 15 days

9.Tab Multivitamin po 1-0-0 x 15 days

10.Syp Vit D3 60 k once a day for 3 days and then once a week for 4weeks

11.Syp Cough suppressant 7.5ml po 1-1-1

12. Tab Paracetamol 500mg po 1-1-1 if having fever

*If allergic to HCQ or as alternative Can Prescribe one of the following antiviral

Tab Favipiravir 200mg 9 tabs twice a day on Day 1 followed by 4 tabs twice a day for 7 days (maximum for 14 days)

Tab Lopinavir/ Ritonavir 200/50mg po 2-0-2 x 7 days OR

For Moderate Symptomatic Covid patient

Rx

Oxygen therapy as per requirement to maintain SpO2 95 % or above

1. Tab Favipiravir 200mg 9 tabs twice a day on Day 1 followed by 4 tabs twice a day for 7days OR Inj Remdesivir 200 mg IV on day 1 followed by 100 mg IV daily for 4 days
2. Tab Doxycycline 100mg 1 -0- 1 x 7 days and
3. Tab Ivermectin 12mg 1-0-0 x 3 days
4.. Inj. Cefoperazone/ sulbactam 1.5gm IV 1 -0- 1 infuse over 30-60 mins.
5. Inj Methylprednisolone IV 0.5 to 1 mg / kg / day for 5-7 days
6. Inj Low molecular weight heparin 0.6 iu s.c daily.*
7. Inj Vit C 1.5 gm IV 1 -0- 1
8. Inj vit D3 6 lac unit IM stat dose.
9. Inj Ondansetron 40 mg IV 1 -0- 1.
10. Inj Pantoprazole 40 mg IV 1 -0- 1.
11. Cough Syp 7.5ml po 1-1-1
12. Tab Zinc 50mg po 1-0-0
13. Tab Magnesium 500mg po 1-0-0
14. Tab Selenium 100 mcg po 1-0-0
15. Inj Multivitamin IV 1-0-0
16. Inj Paracetamol 1gm IV 1-1-1 SOS for fever.

*to be given twice a day if D-Dimer is high

12 ICU management of severe COVID patients

Introduction

COVID-19 patients present with a highly variable wide range of clinical symptoms. Over 3,750,000 individuals have been reported to have a confirmed diagnosis of the illness and the death toll of approximately 2,50,000 has been reported worldwide, across over 200 countries or towns or territories [1]. Approximately 14% of the confirmed cases progressed to developing severe illness and the overall mortality rate has been 4.2% [2]. The main clinical presentation of severe COVID-19 is hypoxic respiratory failure. Patients with severe disease may also progress to developing progressive multiple organ failure. Currently there are no specific treatments available and management is mainly supportive. However, a timely management may prevent the advent of serious complications. In this chapter we will discuss the principal elements of intensive care unit (ICU) management of the severely and critically ill patients.

Clinical Categorization

A. Severe Illness: Individuals with COVID-19 are said to have severe illness when presenting with:

a. dyspnea with a respiratory rate (RR) of ≥30 breaths/min,

b. oxygen saturation (SpO2) ≤90% in room air,

c. and/or lung infiltrates involving 50% lungs [3].

A significant percentage of these cases require admission into the intensive care

unit (ICU) due to development of acute respiratory distress syndrome (ARDS). Among cases with severe illness, the median time to dyspnea from illness or symptom onset has been found to be 5-8 days; the median time to ARDS has been found to be 8-12 days and 10-12 days for ICU admission [4-7]. A majority of patients with severe illness have shown to experience a 'cytokine storm syndrome' due to the host's uncontrolled and generalized inflammatory response [6].

B. Critical illness

a.ARDS

i. Chest imaging shows bilateral opacities, that cannot be fully explained by effusions, lobar or lung collapse, or nodules. Chest X-ray/HRCT shows pulmonary infiltrates involving >50% lungs; not caused by cardiac failure or fluid overload, 2 D Echo rules out hydrostatic cause of the infiltrates

ii. Oxygenation impairment:

Mild ARDS: PaO2/FiO2 of 200-300 mmHg (with PEEP or CPAP ≥5 cm H2O)

Moderate ARDS: PaO2/FiO2 of 100-200 mmHg (with PEEP ≥5 cm H2O)

Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥5 cm H2O).

b.Sepsis:

When a patient demonstrates acute life-threatening organ dysfunction. Signs of organ dysfunction include:

i. altered mental status,

ii. difficult or fast breathing, low oxygen saturation,

iii. reduced urine output,

iv. fast heart rate/ weak pulse/ cold extremities/low blood pressure,

v. skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia.

c. Septic shock: Cases where hypotension is persistent despite volume resuscitation and requiring vasopressors to maintain a mean airway pressure

(MAP) of ≥65 mmHg and serum lactate level of > 2 mmol/L.

Risk factors associated with deterioration and ICU admission

- Age (>60 years)
- Comorbidities (especially diabetes and cardiovascular disease including hypertension)
- Lymphocytopenia with Neutrophil to Lymphocyte ratio >17
- PaO2/FiO2 < 300
- Pulse >100 beats/minute or < 55 beats/minute
- RR > 30 breaths/minute
- New electrocardiogram (ECG) abnormalities
- Deteriorating complete blood count (CBC), liver function profile (LFT) and creatinine test results.
- Reduced urine output.
- C-reactive protein (CRP) > 100 mg/L, lactate dehydrogenase (LDH) >450, D-dimer >1000 ng/ml, Serum Ferritin >300 microg/L.

Criteria for ICU admission

- PaO2 < 60 mmHg in room air or oxygen saturation (SpO2) <85% on supplemental oxygen of 6l/minute.
- Multiple lobar infiltrates
- Thrombocytopenia
- Uremia
- Need for mechanical ventilation
- Hypotension requiring fluid rehydration
- Need for vasopressors

- Confusion
- Hypothermia

Core pathologic processes leading to disease progression

The SARS-CoV-2 attaches to the angiotensin converting enzyme 2 (ACE 2) to gain entry into the host cells. Since these receptors are expressed in vascular endothelial lining of the lower respiratory tract, COVID-19 patients show predominant respiratory symptoms. The reason underlying the extremely variable clinical course, ranging from asymptomatic to severe illness, including ARDS has been attributed to the 'Cytokine storm syndrome'. Observations recorded by Huang et al. in a study involving 41 patients with COVID-19 in Wuhan, showed a cytokine profile similar to secondary hemophagocytic lymphohistiocytosis (sHLH), a hyper inflammatory condition that is triggered by viral infection [4]. Patients admitted in the ICU showed higher levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor alpha (TNFα). Another study confirmed the role of an underlying hyperinflammatory process indicated by higher serum levels of C-reactive protein (CRP), interleukin-6 (IL-6) and Ferritin in patients that had died [9]. The observed hypercytokinemia, results from the systemic spread of a localized immune response to the viral infection [10].

The dysregulated immune system, further results in activation of vascular endothelial cells and endothelial injury leading to formation of micro and macro blood clots [11-14].

Pulmonary inflammation due to the cytokine storm, together with thrombus formation leads to diffuse alveolar damage, fibrin exudates and fibrotic healing. Oxygen absorption is largely impaired causing oxygenation failure and ARDS [15].

The dysregulated production of cytokines may also damage multiple organs, namely kidneys, brain and heart and trigger secondary infections such as bacterial pneumonia.

Patients with underlying coronary artery disease, obesity, cancer, primary immunoglobulin deficiencies, autoimmune conditions, as well as those receiving immunosuppressive therapies are particularly at a high risk for

cytokine storm and severe COVID-19.

Management and treatment guidelines

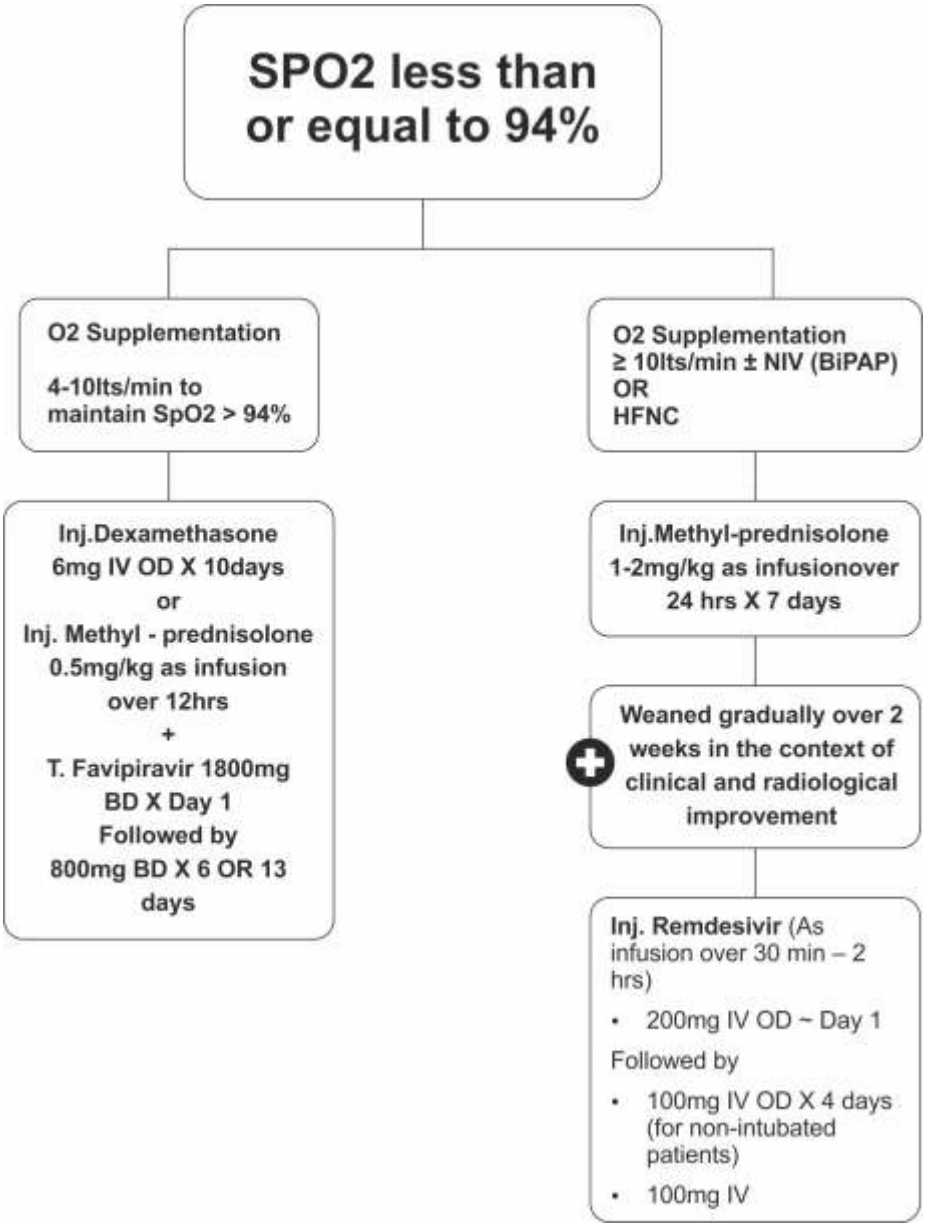

Table 1 - Management Guideleines

In view of the underlying pathology, initiation of anti-inflammatory and anticoagulant treatments must be employed in severe cases before they progress

to multiple organ failure.

A. Anti-inflammatory treatments:

a. Corticosteroids

A study including 26 patients with severe illness showed that the use of methylprednisolone (1-2 mg/kg/day for 5-7 days) correlated with shorter oxygen use duration and improvement in radiographic signs [16] . Use of corticosteroids in ARDS has shown to reduce mortality and mechanical ventilation [17]. It has also been associated with faster resolution of shock.

Dosage: Inj. Methylprednisolone 1-2 mg/kg/day for 5-7 days.

Or

Inj. Dexamethasone 0.2-0.4 mg/kg for 5-7 day

b. IL-6 blocker (e.g. Tocilizumab)

In severely ill patients with an extreme immune response, inhibition of IL-6 may help reduce the cytokine concentrations and attenuate the cytokine storm. Although the cytokine storm is associated with several proinflammatory cytokines, IL-6 is the most important. Anti IL-6 blockers have emerged as an important treatment regimen. A study including 100 severe cases of COVID-19 with complications of ARDS and hyperinflammatory syndrome, administration of Tocilizumab was associated with significant clinical improvement [18].

Tocilizumab

Special considerations before its use include:

i. Presence of raised inflammatory markers (e.g., CRP>20, Ferritin>300, IL-6>20)

ii. Check procalcitonin level which should be less than 0.5.

iii. Active infections and Tuberculosis should be ruled out before use.

iv. Patients should be carefully monitored post Tocilizumab for secondary infections, fungal infections, persistent fever 101 F, neutropenia and leukocytosis.

v. As Tocilizumab is an IL 6 receptor inhibitor, repeat IL 6 level is expected to rise.

Dosage: 8mg/ kg (maximum 400 mg at one time) given slowly in 100 ml NS over 1 hour; dose

can be repeated once after 12 to 24 hrs.

OR

Itolizumab :

Itolizumab, an anti-CD6 IgG1 monoclonal antibody, is used for treating chronic psoriasis. In vitro studies have shown that it inhibits the proliferation of T cells thereby, reducing the production of proinflammatory cytokines. An earlier randomised controlled study in Cuba involving 19 elderly cases with moderate to severe COVID-19 with comorbidities demonstrated a reduction in the IL-6 levels and its administration was also associated with decrease in the risk of ICU admission [19].

The approval followed a randomized controlled trial in India including 20 patients with moderate to severe ARDS. The study demonstrated reduced mortality rate in moderate to severe COVID-19 cases and also improvement of lung function parameters, PaO2 and SpO2 and reduction of inflammatory biomarkers including IL-6, TNF-α, serum Ferritin, D-dimer, LDH and CRP

Indicated when IL-6 levels are 50-100 fold higher than normal levels, worsening trend of the inflammatory markers (Ferritin, LDH, CRP), clinical condition is deteriorating (more than 25% deterioration of PaO2/FiO2 from the immediate previous value).

It has been found to be safe and well tolerated with a minor adverse event of chills at the time of administration.

But, contraindicated in presence of active infections (systemic bacterial/fungal), high serum Procalcitonin, tuberculosis, active hepatitis, absolute neutrophil count < 2000/mm3 and platelet count <1,00,000/mm3, hepatic and renal impairment; patients on chronic steroid therapy, patients <18 years old, pregnant and lactating women.

Dosage: First dose of **Inj.Itolizumab** 1.6mg/kg IV infusion followed by weekly 0.8 mg/kg dose infusion over 4 hours if required.

c. Intravenous (IV) antioxidants such as Vitamin C

Reduction of the cytokine storm is of crucial importance as it can prevent deterioration of a severe COVID-19 patient due to multi organ involvement. IV administration of large doses of Vitamin C has shown clinical benefits in viral ARDS and influenza [20, 21]. It acts by building immunity, reducing the cytokine storm, and inhibition of oxidative processes [22].

Dosage: Inj. Vitamin C 1.5GM IV 6 hourly for 5 days.

d. IV immunoglobulin (Ig) therapy

IV Ig may be used for its immunomodulatory actions.

Initiation of the therapy within 48 hours of ICU admission can reduce the length of ICU stay, use of mechanical ventilation and mortality [23].

B. Anticoagulation treatments:

The dysregulated immune system results in activation of the vascular endothelial cells leading to formation of micro and macro blood clots. To avoid it (or in cases where D-dimer levels are high), anticoagulation treatments are recommended e.g Low molecular weight Heparin (LMWH) or unfractionated Heparin, rTPA

Dose: Start Low molecular weight heparin 0.6 U subcutaneously (SC) OD and if D-dimer is raised make it twice a day. (Check PT/ INR before giving) OR

unfractionated Heparin 5000 Units SC BD

OR

rTPA 50 mg over 3 hours

Contraindicated in case of active bleeding, emergency surgery, platelets platelets < 20,000/mm3, BP >200/120 mmHg and end stage renal disease.

C. Antiviral treatment:

The prolonged detection of SARS-CoV-2 RNA from the respiratory tract of severe cases of COVID-19 necessitates use of antivirals to reduce the viral load. Since, there are no direct acting antivirals developed currently, those that have been used for other conditions have been proposed for improving clinical

outcome (e.g. remdesivir). Among all the antivirals, Remdesivir together with regular treatment has shown the most promising results in moderate to severe COVID-19. [24].

Remdesivir

Indication: It may be considered in patients with moderate - severe disease (those on oxygen)

Following are the **contraindications:**

1. AST/ALT > 5 times Upper limit of normal (ULN)
2. Severe renal impairment (i.e., eGFR < 3Oml/min/m2 or need for haemodialysis)
3. Pregnancy or lactating females
4. Children (< 12 years of age)

Dose: 200 mg IV Remdesivir on day 1 followed by 100 mg IV daily for 4 days (Total 5 days)

Consent: Written informed consent from patient before administration

D. Antibiotics:

Secondary bacterial infection in COVID-19 patients may be difficult to identify because the symptoms may be similar to the underlying viral infection. Since, superadded infection has been reported in this population [25] and it may increase the risk of mortality, it is recommended to initiate empiric antimicrobial treatment (e.g. injection meropenem, magnex forte, piptaz or targocid, tablet doxycycline) in seriously and critically ill COVID-19 patients. Check procalcitonin levels which indicates superimposed secondary infection. One cannot rely only on total WBC count because it can be raised due to corticosteroids also.

Inj. Meropenem 1 gm IV TDS

OR

Inj. Cefoperazone-Sulbactum forte 1.5gm IV BD infused over 15-60 mins.

OR

Inj. Piperacillin-Tazobactum 3.375 g IV q6hr infuse over 30 mins, for 7-10 days

OR

Inj. Teicoplanin

Moderate infections:

Loading dose - Single iv injection of 400mg on the first day.

Maintenance Dose - Single iv injection of 200mg daily. Infusion over 30 mins

Severe infections:

Loading dose - Three iv injections of 400mg administered 12 hours apart.

Maintenance Dose - Single iv injection of 400mg daily. Infusion over 30 mins. Check Cr.Cl.

E. Antipyretics:

Acetaminophen or paracetamol have a known safety profile and are effective in fever management. Use of non-steroidal anti-inflammatory drugs (NSAIDs) is highly debated as they may upregulate ACE2 receptors, the entry point of the virus and hence to be avoided.

Dose: Tab. 500 mg upto 4 times a day with at least 4 hours between doses.

F. Convalescent plasma therapy:

Refer to the previous chapter for details

G. Supportive Treatment:

a.Tab Zinc 50 MG 0-1-0 for 7 DAYS

b.Inj. Vitamin C 1.5GM IV 6 Hourly for 5 days

c.Tab N-Acetyl Cysteine TDS

d.Inj vit D3 3-6 lac unit IM stat dose.

e.Inj Multivitamin IV once a day

f.Melatonin 6-12 mg at night (optional).

g.Thiamine 200 mg IV q 12 hourly

h.Mg levels must be monitored to keep the levels between 2.0 and 2.4 mmol/l. Hypomagnesemia increases 'cytokine storm' and prolongs Qtc [26-28]

Dose: 2 g stat IV.

To summarise, a **'MATH+'** treatment is recommended. This includes methylprednisolone; IV ascorbic acid; thiamine; heparin. Additional treatment components include, famotidine in renal impairment; zinc; vitamin D; magnesium; melatonin; broad spectrum antibiotics if superadded bacterial pneumonia suspected on the basis of procalcitonin levels and respiratory tract culture; rehydration with 500 ml boluses of Lactate Ringers in case of volume depletion; norepinephrine for hypotension; and optionally azithromycin, simvastatin and remdesivir/favipiravir.

H. Respiratory Support/Oxygen Therapy

Intubation must be avoided as far as possible as it can worsen lung injury mainly due to regional lung overdistension, infiltration of inflammatory cells, increase in vascular permeability and pulmonary edema. These also contribute to multi-organ failure [29]. Immediate supplemental oxygen therapy is to be initiated in patients with severe illness and respiratory distress, hypoxemia or shock. As per the national guidelines targeting SpO2 of minimum 90% (92-96% in pregnant patients) is recommended. Strategies that are used include:

a. **Supplemental oxygen with a high flow oxygen mask / Non rebreather mask-NRBM** (10-15 L/min).

b. When respiratory distress or hypoxemia cannot be alleviated through the above, **high flow humidified oxygen through nasal cannula (HFNO)** (up to 30-60 l/min) OR non-invasive mechanical ventilation may be considered.

There are several advantages of an HFNO:

i. Heated and humidified, high flow oxygen is delivered generating low levels of positive pressure in the upper airways [30-32].

ii. It generates a more stable inspired fraction of oxygen.

iii. Decreases the physiological dead space by flushing out CO2 from the upper airways [33].

iv. High flow nasal cannula is recommended over non-invasive mechanical ventilation as it is associated with a lower incidence of intubation in acute hypoxemic respiratory failure [34].

c. **Monitor** must be attached to allow continuous monitoring of SpO2, pulse, blood pressure, respiratory rate.

d. **Awake proning**. Prone positioning reduces lung compression [35], improves perfusion [36], and makes ventilation more homogeneous by reducing ventral alveolar distension and dorsal alveolar collapse thereby decreasing the difference between the ventral and dorsal transpulmonary pressures [37]. Prone positioning in patients with moderate to severe ARDS has been found to be associated with reduced mortality [38].

Indications for awake proning include:

i. In cases where there is an expectation that the patient has a fairly reversible lung injury and may avoid intubation.

ii. Absence of hypercapnia or substantial dyspnea.

iii. Normal mental status so that the patient is able to communicate distress.

iv. No risk of airway obstruction or difficulty.

In these cases 16-18 hours of proning is recommended. Thorough aerosol precautions must be followed while proning and utmost precautions to avoid disconnection of the ventilator circuit to be taken.

e. BiPAP

Before invasive mechanical ventilation (intubation) give a trial with bilevel positive airway pressure (BiPAP). The advantage of BiPAP is that it is non-invasive. The lung injury induced by use of mechanical ventilation can be avoided with use of BiPAP. Also, the patient can talk and take drugs orally. But despite BiPAP, if patient displays signs of worsening respiratory insufficiency or deterioration, namely increased RR>30 breaths/minute, systolic blood pressure < 90mmHg despite IV fluids and vasopressors, respiratory acidosis, persistent hypoxia (SpO2 < 88% on high flow mask), poor oxygenation

(PaO2/FiO2<150 mmHg) after 2 hours of HFNO (or NIV) and Glasgow Coma Scale (GCS) less than 8 (drowsy/ semi conscious/unconscious), intubation may be considered.

Fig 1 - Mechanical Ventilation

f. Mechanical Ventilation: Intubation must be planned and conducted with adequate sedation and neuromuscular paralysis. For mechanically ventilated patients, using lower tidal volumes (4-8 ml/kg predicted body weight; PBW) and lower inspiratory pressures (plateau pressure of <30cm H2O) is recommended for patients with ARDS and sepsis induced respiratory failure to minimise lung injury. Hypercapnia is permitted as long as pH goal of 7.3-7.45 is achieved. In patients with moderate and severe ARDS, higher PEEP is suggested.

After intubation check for lung compliance on ventilator and use following ventilator setup and adjustment:

i. Volume A/C mode on the ventilator is selected.

ii. To calculate PBW the formula given is used

Males: 50 + 2.3 [height (inches)-60]

Females: 45.5 + 2.3 [height (inches)-60]

iii. Ventilator settings so as to achieve the initial (low tidal volume) VT:6 mL/kg (PBW)

iv. The initial rate is set to the approximate baseline minute ventilation (not >35 bpm). A pH of over 7.2 is targeted. The PaCO2 may rise even with an RR of 35, in that case the dead space is reduced in the circuit. If the pH drops below 7.2, sodium bicarbonate infusion may be considered.

v. VT and RR are adjusted to achieve a target pH of 7.2 and plateau pressure (Pplat) goal of < 30 cm H2O. If Pplat continues to be >30 cm, VT is deceased by 1 ml/kg steps (minimum:4 ml/kg).

vi. Use a positive end-expiratory pressure (PEEP) of 5-10 cms of water with BP monitoring,

vii. FIO2 of 60 – 70% to maintain SpO2 > 85 and PaO2 > 60 mm Hg,

viii. Pplat (0.5 second inspiratory pause) is checked at least every 4 hours and after each change in PEEP or VT.

I. Hemodynamic support and management of septic shock

a. The incidence of septic shock is around 20-35% among COVID-19 patients admitted in the ICU. Conservative fluid management is recommended in patients with severe illness even when there is no evidence of shock. Cautious rehydration with 500 ml boluses of Lactate Ringers is recommended.

b. If in confirmed or suspected COVID cases, vasopressors are needed to maintain the MAP ≥ 65 mmHg and lactate is > 2mmol/L in the absence of hypovolemia, septic shock has ensued.

c. Following treatments must be started within one hour of identification:

i. Antimicrobial therapy and fluid loading.

ii. Use of norepinephrine as the first line vasoactive agent. Use of corticosteroids has also been found to be associated with shorter time to resolution of shock and ICU stay [39, 40].

iii. In resuscitation from septic shock, at least 30 ml/kg of isotonic crystalloid is given in the first 3 hours. Crystalloids contain normal

saline and Ringer's lactate.The target is to achieve MAP >65 mmHg, urine output >0.5 ml/kg/hr and improvement of skin mottling, capillary refill, consciousness and lactate.

iv. Trial of inhaled Flolan (epoprostenol), a pulmonary arterial vasodilator. In severe ARDS and hypoxemia and mechanically ventilated cases a trial of pulmonary vasodilator is recommended as rescue therapy. However, if no instant improvement in oxygenation is observed, the treatment may be tapered off to avoid rebound pulmonary vasoconstriction.

J. Monitoring

a. Daily monitoring of CBC, electrolytes, LFT, creatinine, procalcitonin, CRP, IL-6, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Troponins, brain natriuretic peptide (BNP) and Magnesium levels. CRP, IL-6 and Ferritin particularly are markers that track disease severity closely. It has been observed that the levels of CRP at initial and progression stages are higher than those in the mild cases. Also, early CRP levels are closely associated with the CT score

b. Chest CT. Crazy paving and consolidation patterns are seen in severe cases of COVID-19. On a scale of 0-25, severe COVID-19 patients have a CT score falling between 11-14; those that are critically ill have a score in the range of 15-24. A CT score of ≥ 18 (on a scale of 0-25) has shown to be associated with mortality.

CT scans are not to be repeated, follow up is done on chest radiograph and/or chest ultrasound.

c. 2D-ECHO to be monitored closely since patients tend to develop severe cardiomyopathy.

K. Criteria for extubation

Parameters that may guide weaning off a patient from mechanical ventilation include:

a. RR < 25 breaths per minute

b. Tidal volume > 5 mL/kg

c. Vital capacity > 10 mL/kg

d. Minute ventilation < 10 L/min

e. PaO2/FIO2 > 200

f. Shunt (Qs/Qt) less than 20%

g. Negative inspiratory force (NIF) less than (more negative) -25 cm water

L. Criteria for transfer out of the ICU

a. Absence of respiratory distress

b. Oxygen saturations ≥ 90 % on FIO2 ≤ 50 %

c. Systolic BP ≥ 100 mmHg and ≤ 220 mmHg for 24 hours

d. Heart rate between 50 and 110 beats per minute

e. No need for vasopressors for 24 hours

f. No need for fluid resuscitation for 24 hours

g. No evidence of hypo-perfusion; confusion; or cold, cyanotic extremities, and poor capillary refill; metabolic acidosis; or poor urine output.

h. Stable GCS.

i. Neurologic checks less frequent than every hour

j. No evidence of new, un-treated infections.

k. No deterioration of renal function in the last 24 hours.

M. Post ICU management

a. LMWH 0.4-0.6 Units SC daily or Tab Aspirin

b. IV Methylprednisolone/tab prednisone 40 mg day, then weaned slowly

c. Vitamin C 1 gm po BD

d. Multivitamin 1 tab po OD

e. Zinc 50 mg po OD

f. Magnesium 500mg po OD

g. Vitamin D 60 K once a week

h. Melatonin 3-6 mg at night

i. Protein supplement

N. Rehabilitation

Rehabilitation can reduce complications associated with ICU admission and also facilitate a quicker recovery. Intervention is aimed at addressing the pulmonary, neurological, physical, cognitive, swallowing and psychological impairments.

General principles that may be employed:

a. Body position management and expectoration training when difficulty in expectoration

b. Breathing exercises (diaphragmatic breathing) and expiration exercises

In case SpO2 < 88% or patient develops signs such as palpitations, sweating, chest tightness or shortness of breath, discontinue rehabilitation.

c. Reduction of complications of immobilisation, e.g. stretching

d. Prevention of secretion retention

e. Patients with GCS ≤ 8 are given passive mobilisation and pronation.

f. Psychological counseling to relieve anxiety and depression

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Sample Prescription

Rx

Oxygen therapy as per requirement to maintain SpO2 95 % or above

1. Inj. Meropenem 1 gm IV TDS
2. Inj Remdesivir 200 mg IV on day 1 followed by 100 mg IV daily x 4 days
3. Inj Methylprednisolone IV 1-2 mg/kg/day x 5-7 days.
4. Inj Tocilizumab 400 mg at one time given slowly in 100 ml normal saline over an hour (when IL6 > 100 and normal pct level)
5. Inj. LMWH 0.6 U SC OD per day (if D dimer high make it BD)
6. Tab Doxycycline 100mg bd x 7 days and
7. Tab Ivermectin 12mg od x 3 days
8. Inj Pantoprazole 40 mg IV twice a day.
9. Inj Ondansetron 40 mg IV twice a day.
10. Inj Vit C 3 gm IV twice a day
11. Tab Zinc 50mg po once a day
12. Tab Magnesium 500mg po once a day
13. Tab Selenium 100 mcg po once a day
14. Inj Multivitamin IV once a day
15. Inj Vit D3 6 lac unit IM stat dose
16. Inj Paracetamol TDS SOS for fever

13 Pediatric Management of COVID-19

1. Introduction

Pediatric population is defined as being less than 18 years old. Fewer cases have been reported among children than among adults globally. Most cases in children are mild requiring symptomatic care alone. But, in infants and younger children, there has been a tendency for more severe illness than older children. In this chapter we have attempted to provide guidelines for management of pediatric COVID-19 cases.

2. Epidemiology

COVID-19 caused by SARS-CoV-2, mainly spreads from close contact with infected persons (from hands to eyes, nose or mouth) and from respiratory droplets released when an infected person coughs or sneezes or talks. Aerosol transmission may be another mode of spread. Although initially, vertical transmission or mother-to-fetus intrauterine transmission was said to be absent but lately evidence of vertical transmission have been frequently reported [1]. There is no evidence of transmission through breastfeeding.

3. Triage

The purpose of a triage is discussed in the earlier chapters.

Identification of pediatric cases that are suspected/confirmed to have the infection if:

A. Suspected cases

A child was a close contact of confirmed COVID-19 case OR is from an area or community where COVID-19 cases have been reported and presents with the following symptoms:

a. fever or respiratory symptoms such as cough or shortness of breath or digestive symptoms such as vomiting, nausea or diarrhea or fatigue and;

b. Normal or decreased WBC count with decreased lymphocyte count or increased CRP;

c. Abnormal chest radiograph.

B. Confirmed cases

A child is said to be a confirmed case of COVID-19 infection on the basis of laboratory confirmation.

4. Signs and Symptoms

Fever and cough are the commonest symptoms. But, these symptoms may not always be present. Other symptoms include:

- Shortness of breath
- Nasal congestion or rhinorrhea
- Sore throat
- Myalgia
- Diarrhea
- Fatigue
- Rash
- Abdominal pain
- Diarrhea, nausea or vomiting

Among neonates fever and cough are the most common symptoms. Other reported symptoms include:

- Fever

- Lethargy
- Rhinorrhea
- Tachypnea
- Increased work of breathing
- Vomiting
- Diarrhea
- Poor feeding

5. Diagnosis

Diagnosis is confirmed by RT-PCR on nasopharyngeal and oropharyngeal swab.

A. Laboratory findings

The following abnormalities have been noted in this age group:

- Lymphopenia
- Increase levels of liver enzymes
- Increase levels of lactate dehydrogenase (LDH)
- Elevated CRP
- Elevated erythrocyte sedimentation rate (ESR)
- Elevated procalcitonin levels

B. Radiographic findings

Although, chest X-Ray is not as sensitive as a chest computed tomography (CT), but, it may be useful in evaluating progression or resolution. It is also more relevant in the pediatric population since they have higher radiation sensitivity and chest CT is not recommended in pediatric patients. However, in cases such as those that have worsening clinical symptoms or those with elevated D-dimer, chest CT may be done.

The most common finding on chest X-ray that has been seen is bilateral ground glass opacities (GGO) and/or consolidation that are mainly peripheral and/sub pleural, predominantly in the lower lung zone. In the earlier stages, though, unilateral GGO have been seen [2].

Chest CT findings: This population demonstrates a significantly lower rate of positive CT findings. Where involvement is present, less number of pulmonary lobes is involved with a lower overall lung score.

In cases where abnormalities are detected on CT, the most common findings that have been noted are bilateral, peripheral and/or subpleural GGO and/or consolidation mostly in the lower lobes [3].

6. Clinical categorization

A. **Asymptomatic:** When the diagnostic test is positive with absence of clinical signs and symptoms and normal chest X-ray.

B. **Mild:** Mild cases include children with an uncomplicated upper respiratory tract infection. This may include symptoms such as fever, cough, sore throat, nasal congestion, malaise, or headache.

   Pediatric cases with mild illness are treated at a COVID Care Centre.

C. **Moderate:** Children presenting with features of dyspnea and or hypoxia with SpO2 of < 94% (range 90-94%) in room air, along with fever, cough, respiratory rate (RR) ≥ 24 breaths/minute (in babies < 2 months: ≥ 60 breaths/minute; in babies 2-11 months: ≥ 50 breaths/minute; in children 1-5 years of age: ≥ 40 breaths/minute) are said to have moderate illness.

Pediatric cases with moderate illness are treated in a Dedicated COVID Heath Centre.

D. **Severe:** Pediatric cases presenting with cough or difficulty in breathing, plus at least one of the following:

a. Central cyanosis or SpO2 <90% in room air.

b. Signs of severe respiratory distress such as grunting, in-drawing of chest, RR in babies <2 months old ≥60 breaths/minute; in babies 2–11 months old ≥50 breaths/minute; children 1–5 years old ≥40 breaths/minute.

c. Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.

E. Critical illness:

a. Pediatric Acute respiratory distress syndrome (PARDS)

Oxygenation Index (OI) or Oxygenation Index using SpO2 (OSI) is used to assess hypoxemia in children.

OI- (FiO2 × mean airway pressure (Paw) × 100)/PaO2

and

OSI- (FiO2 × Paw × 100)/SpO2

Pediatric cases on non-invasive mechanical ventilation are said to be at risk of PARDS if :

i. Those receiving oxygen support through mask/nasal cannula/high flow, SpO2 88-97% with oxygen support at minimum flow (<1 year: 2 L/min, 1-5 years: 4 L/min; 5-10 years: 6 L/min; >10 years: 8 L/min).

ii. Those receiving respiratory support through nasal mask CPAP or BiPAP; FiO2 ≥ 40% to achieve SpO2 of 88-97% [4].

OI is used to identify PARDS, but if partial pressure of arterial oxygen (PaO2) is not available, oxygen saturation (SpO2).

- Mild PARDS:

OI: 4-8 or OSI: 5-7.5 (invasively ventilated)

- Moderate PARDS:

OI: 8-16 or OSI: 7.5-12.3 (invasively ventilated)

- Severe PARDS:

OI: ≥ 16 or OSI ≥ 12.3

b. Sepsis and septic shock:

Definition of sepsis is similar to adults. But, in children, a systemic inflammatory

response including an abnormal temperature or abnormal leukocyte count is seen as part of the clinical presentation. In addition, there are age-specific normative values for vital signs [5].

Some of the red flag signs include:

- Decreased mental status
- Cold extremities
- Delayed capillary refill
- Weak pulse
- Low urine output
- Hypotension; the lower limit of Systolic BP by age being: < 1 month- 60 mmHg; 1 month to 10 years-70+ (2 × age in years); ≥ 10 years- 90 mm Hg.

7. Clinical Management and Treatment guidelines [6]

A. Management of mild cases

Symptomatic treatment is initiated. This includes:

a. Antipyretics (Paracetamol) for fever and myalgia

b. Adequate nutrition and appropriate hydration

Monitoring for signs or symptoms of clinical deterioration, namely fast breathing or shallow breathing (grunting or inability to breastfeed in infants), bluish discoloration of lips/ face, chest pain, confusion is required. In case of any of these, hospital admission is required.

B. Management of moderate cases

a. Symptomatic treatment, e.g. paracetamol for fever and antitussives for cough.

b. Adequate nutrition and hydration needs to be ensured.

c. Oxygen supplementation to target and maintain SpO2 ≥ 97%

d. Close monitoring of these cases is required for signs of deterioration. Most

recover without deterioration.

But, corticosteroids (preferably dexamethasone) is recommended:

i. in those requiring oxygen support, or

ii. in those with underlying conditions requiring steroids.

Dose: 0.15 mg/kg once daily (max: 6mg) for up to 10 days

e. Antiviral therapy:

Inj Remdesivir. (Only if oxygen support is required. Not given in children <12 years).

Dose: <40 kg- one loading dose of 5mg/kg on the first day followed by a maintenance dose of 2.5 mg/kg for 5-10 days depending on response.

≥ 40 kg-one loading dose of 200 mg on the first day followed by 100 mg for 5-10 days depending on response.

f. Empiric antibiotics are started if bacterial infection is suspected.

g. IL-6 inhibitor (Tociluzumab):

For cases with a high risk of cytokine storm indicated as below:

i. IL-6 ≥ 3 times upper normal limit,

ii. Ferritin ≥ 300 ug/L doubling in 24 hours,

iii. LDH > 250; iv. Elevated D-dimer.

OR

Presence of Pulmonary infiltrates

and

SpO2 ≤ 93% on RA or on oxygen support> 6L/min

Dose: < 30 kg: 12 mg/kg X 1 (Max 800 mg); ≥ 30 kg: 8 mg/kg X 1 (Max 800 mg). Single dose but if required may be repeated after 8-12 hours.

h. Anticoagulation:

Currently there are no specific recommendations for pediatric patients with COVID-19. Risk factors for thromboembolism should be assessed on admission and then reassessed every 48-72 hours during hospitalization. Anticoagulation prophylaxis should be considered in at risk cases unless contraindicated.

C. Management of severe cases.

They are to be admitted in the NICU or PICU

a. Symptomatic treatment with paracetamol and antitussives to continue

b. Continuous monitoring with pulse oximeters is necessary.

c. Conservative fluid management

d. Corticosteroids:

IV Methylprednisolone 1-2 mg/kg

or

Dexamethasone 0.2-0.4 mg/kg for 5-7 days

e. Children should be administered oxygen therapy to target SpO2 ≥94%.

f. Shock:

Within 1 hour of recognition:

- Antimicrobial therapy is initiated,
- Fluid loading and
- Vasopressors for hypotension to achieve an age specific target of mean arterial pressure.
- In case of septic shock, 20 ml/kg of isotonic crystalloid as rapid bolus and then up to 40-60 ml/kg in the first hour is to be given.

If there are signs of volume overload then fluid administration may need to be reduced or discontinued. Oxygen support ought to be given to target SpO2 ≥94% during resuscitation.

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14 Post Covid Management

COVID-19 may be capable of inflicting long-term damage to most organs of the human body mainly the lungs, heart, and nervous system. Researchers are also studying its effect on kidneys, liver, and gastrointestinal tract. Clinicians have also reported that the recovery of patients to their former health is slow. These are not only severely affected patients but also mild and moderately affected patients. 10% of affected individuals experience prolonged illness.

Patients recovering from Covid-19 who are discharged from hospital need care and support as many of them continue to experience fatigue, shortness of breath chest pain, reduced exercise tolerance, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption, thromboembolic conditions and persistent psychological difficulties as a result of their experiences of illness and treatment.

Management

- Holistic support, rest, symptomatic treatment, and gradual increase in activity can help in fast recovery of patients after discharge
- Home pulse oximetry can be helpful in monitoring breathlessness
- Indications for specialist assessment include clinical concern along with respiratory, cardiac, or neurological symptoms that are new, persistent, or progressive.
- One of the most common problems faced during post-COVID-19 recovery is lung fibrosis. Lung damage caused initially due to the infection may later lead

to scarring of lungs. This affects the overall quality of life of the patient. This condition requires the support of home oxygenation even after discharge and recovery. In some cases, lung fibrosis may also lead to cardiac complications. Pulmonary rehabilitation and graded exercise programmes may aid functional recovery in these patients. Antifibrotic drugs such as Pirfenidone and Nintedanib may be used.

- For patients who suffered a significant respiratory illness a chest X ray should be ordered at 12 weeks and checked for new, persistent, or progressive symptoms.

- Pulmonary Thrombo Embolism (PTE) is another pulmonary condition experienced by Covid patients in the recovery period. It refers to a blockage or clot in the pulmonary artery, which prevents the oxygen from reaching the lungs. Its prevalence has increased due to restriction of movement during the infection phase. Anticoagulant and antifibrotic drugs are often prescribed alongwith home oxygenation as per requirement.

- Mental health interventions such as CBT and antidepressants may also help tackle psychological issues.

- Breathing exercises are actively encouraged post operatively and could probably be advised to recovering COVID-19 patients as well.

- Good nutrition is essential for better recovery, consumption of fruits and vegetables, along with increased intake of high quality protein to help repair muscles affected during the active COVID19 infection.

- As the focus in the post-acute phase is on the recovery of a patient's respiratory function, cessation of smoking should be encouraged along with avoidance of ibuprofen where possible.

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15 Convalescent Plasma Therapy for COVID-19

Convalescent plasma (CP) therapy is a passive immunization method which has been used to prevent and manage various infectious diseases including other coronovirus infections since the 20th Century. CP is obtained using apheresis in survivors with prior infections caused by pathogens in whom antibodies against the causal agent of disease are developed. It has been considered as an emergency intervention in past pandemics, including the Spanish flu, SARS-CoV, West Nile virus, and Ebola virus. Early administration of CP has shown to reduce mortality in severe acute respiratory infections due to influenza and SARS-CoV as compared to placebo controlled or no therapy group of patients. Convalescent plasma therapy is used off- label for moderate to severe COVID-19 patients.

Acquisition of Convalescent plasma

The recommended procedure to obtain plasma is by apheresis. The donors must undergo assessment before donation to ensure compliance. Donors should be between 18 and 65 years without infectious symptomatology and a negative test for COVID-19 after 14 days of recovery. These tests must be repeated 48 hours later and at the moment of donation too.

Apheresis is done by continuous centrifugation of blood from donor to allow a selective collection plasma. 400–800 mL plasma can be acquired from a single apheresis donation which can be stored in units of 200 or 250 mL, and frozen within 24 h of collection to be used in further transfusions

CP is composed of a variety of blood derived components. It contains a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins

including albumin, immunoglobulins, complement, coagulation and antithrombotic factors. Plasma obtained from a healthy donor provides neutralizing antibodies (Nabs), other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins and other undefined proteins.

Mechanism of Action

The underlying mechanism of CP therapy includes direct neutralization of the virus for eradication, immunomodulation via amelioration of severe inflammatory response by infusion of anti-inflammatory cytokines and antibodies that block complement, inflammatory cytokines and autoantibodies obtained from the donors.

All these benefits of CP are better achieved if used in moderately affected Covid patients

Prerequisites and dosage according to MoHFW

- Convalescent plasma may be considered in patients with moderate disease who are not improving (oxygen requirement is progressively increasing) despite use of steroids.
- ABO compatibility and cross matching of the donor plasma.
- Neutralizing titer of donor plasma should be above the specific threshold (if the latter is not available, plasma IgG titer (against S-protein RBD) above 1:640 should be used).
- Recipient should be closely monitored for several hours post transfusion for any transfusion related adverse events.
- Use should be avoided in patients with IgA deficiency or immunoglobulin allergy
- Dose can be variable ranging from 4 to 13 ml/kg (usually 200 ml single dose given slowly over not less than 2 hour.

Adverse events associated with Convalescent plasma therapy

Majority of the adverse effects associated with plasma transfusion are non-lethal

- Transfusion associated circulatory overload (TACO);

- Allergic/anaphylactic reactions;
- Transfusion related transmission of infections (TTI);
- Febrile non-hemolytic transfusion reactions (FNHTR);
- Hemolytic transfusion reactions (HTR); and
- Rare occurrence of RBC alloimmunization.
- Theoretical risk of using CP includes antibody dependent enhancement of infection

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Section D

Adjuvant Therapies

16 Diet During and After COVID-19 Illness

Eating well and maintaining a healthy weight is important to maintain strength & fitness and to ensure that our body has enough nutrients (energy, protein, vitamins and minerals) to help protect us from infection and recover from illness.

There is no clear information whether individual nutrient deficiency affected immunity or whether nutrient deficiency simply led to a decline in the patients' overall condition.

Hyper-inflammation is a major component in the course of the severe progression of COVID-19 it is clear nowadays, vitamin D, and selenium deficiency should be highlighted.

For proper function of immune system several micronutrients especially vitamin A, C and D; and trace elements such as Zinc and Selenium are essential.

Balanced diet is essential to minimize micronutrient deficiencies and prevent viral infections such as COVID-19.

Indian states with high prevalence of underweight and anaemia have reported the highest number of COVID-19 cases.

Vitamin E is the potent antioxidant and has the ability to modulate host immune functions. Vitamin E deficiency is known to impairs both humoral and cellular immunity

Vitamin A plays an important role in enhancing immune function, and having a

regulatory function in both cellular and humoral immune responses

Vitamin D plays a vital role in modulating both innate and adaptive immune responses. Epidemiological data has linked vitamin D deficiency to increased susceptibility to acute viral respiratory infections.

Vitamin C is known as an essential antioxidant and enzymaticco-factor for many physiological reactions in the body

Zinc is an essential trace element which plays an important role in growth, development, and the maintenance of immune function. Zinc deficiency has been associated with an increased susceptibility to infectious diseases, including viral infections

Selenium is another trace element that plays role of antioxidant and anti-inflammatory effect.

Low selenium status has been associated with an increased risk of mortality, poor immune function, and cognitive decline, while a higher selenium concentration or selenium supplementation has shown antiviral effects

Copper plays a crucial role in immunity by participating in the development and differentiation of immune cells

Magnesium plays an important role in controlling immune function by exerting a marked influence on immunoglobulin syn-thesis, immune cell adherence, antibody-dependent cytolysis, Immunoglobulin M (IgM) lymphocyte binding, macrophage response to lymphokines, and T helper-B cell adherence.

Probiotic supplements

Probiotics are defined as live micro-organisms that confer ahealth benefit to the host, including on the gastrointestinal tract,when administered in adequate amounts

They also stimulateimmune response by increasing the antibody production

Balance the diet:

A well-balanced and healthy diet plays an important role to strengthen the immune system. Diet must be composed of a variety of foods from different food groups

There are three major food groups:

Energy-rich foods:

Energy including foods include carbohydrate and fats.

Sources of carbohydrate includes Cereals like Jowar, dalia (broken wheat), oats, whole wheat flour.

Fats and oils increase calorie density of food Fats to be used for cooking can be primarily soya, til (sesame), rice bran oil, & canola oils.

Avoid taking large quantities of oily foods in the diet. Calorie needs of the body are increased during infection.

Bodybuilding foods:

The foods that provide protein are body building foods. Proteins are structural component of many enzymes and hormones. They support muscle contraction and movement. It provides support to the body and helps keep organs healthy. Protein support our immune system to fight infections. Sources include Eggs, dairy, legumes, pulses dals, & lean meat.

Protective foods:

Protective foods include fruits and vegetables, nuts that are the sources of

vitamins and minerals. Seasonal fruits and vegetables (dark green leafy, yellow and orange colored, citrus, and other fruits) provide protective effect.

Spices and Herbs-

Certain spices like black pepper and clove while preparing food in small amounts and using herbs and spices like kalonji (onion seeds) turmeric, ajwain, ginger, garlic, star anise, nutmeg, oregano, Tulsi & cinnamon may be beneficial. As most of these foods posses antioxidant properties and helps in boosting overall immunity.

Fluids:

- Hydration and nutrition play an important role in the body's response to and recovery from the COVID-19 virus
- Drinking warm water & clear liquid beverages are important even if not thirsty. (include small quantity turmeric water sometimes)
- It is recommended to replace body's fluid losses to thin respiratory secretions.
- Frequent small sips of warm liquids every few minutes would be helpful.

- For vomiting or diarrhea, oral rehydration solution can be consumed in addition to water.
- Use a variety of liquids to avoid taste fatigue.
- Including liquids such as buttermilk (made from freshly set curd), lime water, unsweetened fruit juices, moong dal paani, rasam can be recommended to increase the fluid intake.
- One can Include decoction/ kadha advised by ministry of AYUSH

Tulsi(basil), Dalchini(cinnamon), Kalimirchi black pepper), Shunthi (dry ginger) and munnakka (raisin)- once or twice a day. Add jaggery (natural sugar) and/ or fresh lemon juice to your taste, if needed

Shortness of breath

- In case of dyspnea (shortness of breath), reduce carbohydrate quantity like too much of sweets, juices with sugar & stress on low glycemic index carbohydrates like whole cereals, lentils, beans, green vegetables, fruits like apple, papaya etc.

AVOID

- Avoid packet and preserved food.
- Avoid too much sugary foods.
- Avoid eating fried foods frequently.
- Intake of alcohol & tobacco products.
- Avoid intake of red meat.

Food hygiene and sanitation

At present, there is no evidence of transmission of the virus from food or food packaging. However, it may be possible that people can become infected by touching a surface or object contaminated with the virus and then touching their face.

Foods likes fruits and vegetables should be washed with lukewarm water. Animal meat, poultry and fish should be washed properly and cooked and cooked well before consumption

Precautions to be taken while handling food:

- Wash your hand with soap and water for at least 40 to 60 seconds before handling food
- While handling different types of food
- After finishing food preparation
- Before consuming food
- Consuming a meal, snack or any food item

Guidelines For Breastfeeding

Corona virus has not been found in breast milk.

But if you have Covid-19 or suspected of it then you could spread the virus to your infant through tiny droplets that spread when you talk, cough, or sneeze

Exclusive breastfeeding for six months protects newborns from infections and helps protect them throughout their infancy and childhood.

Breastfeeding increases immunity and provide antibodies to the child from the mother.

It's very important to follow all the necessary sanitary practices liken washing hands with soap and water while handling baby, wearing a mask are important.

Anti-inflammatory Diet

Balanced diet with variety of food reduces inflammation and supports your immune system to help you fight off infections. It also prevents and manage disease, improve energy and get relief from conditions driven by inflammation.

A balanced diet rich in fruit, vegetables, legumes, whole grains, nuts, and monounsaturated fats these foods are associated with anti-inflammatory and immunomodulatory compounds, including essential vitamins like C, D, and E and minerals like zinc, copper, calcium, etc., that affect overall nutritional status of person.

Consumption of Fried foods, Trans fats, Refined carbs, Soda, Sugar, Processed Meats can lead to inflammation in the body

Some important Immunity Boosting and Anti- inflammatory Nutrients and their sources

- ZINC: Zinc is very essential for normal development and function of immune cells.

Food rich in Zinc

Cereal- Ragi, maize, rajgeera, whole wheat

Legumes- Bengal gram dal (chana dal), black gram (urad dal), and Cow pea white (chowli), lentil dal (masoor dal), dry green peas, rajma, Soyabean

Nuts and oil seeds: Almonds, Cashew nuts, Gingelly seeds, Mustard seeds, Sunflower seeds, Chicken and Egg.

- **Vitamin C:** Vitamin C contributes to Immune defense by supporting various cellular functions.

  Foods rich in Vit C: Amla, Guava, capsicum, oranges, papaya, Red amaranth leaves, lemon juice

- **Selenium:** Selenium plays a role in regulating oxidative stress in the body.

  Selenium rich food: egg, Tur Dal, Chana Dal, whole wheat flour, Chana, moong dal, chicken, mackerel fish (Bangada)

- **Iron:** Iron plays an important role of immune cell proliferation and maturation.

  Foods rich in Iron:

  Moth beans, rajma, soybean, rajgeera, dates, raisins, garden cress seeds, chicken liver, radish leaves, spinach

- **Magnesium:** Magnesium acts as cofactor for the immune globulin synthesise

  Foods rich in magnesium: Ragi (nachani), legumes, green leafy vegetables, Almonds, cashews, garden cress seeds, sunflower seeds, black Til.

- **Vitamin E:**

  Vitamin E is an antioxidant that has the ability to modulate host immune functions especially in elderly population.

  Sources of Vitamin E: Almonds, flaxseeds, garden cress seeds, Safflower seeds, pistachio, sunflower seeds.

- **Omega 3 fatty acid:** Omega 3 fatty acids play a very important role of

reducing inflammation and boosts the immune system.

Sources of Omega 3 fatty acid: flaxseeds, Chia seeds, Walnut, Fish

- **Vitamin D:** Vitamin D has numerous effects on cells within the immune system

  Sources of Vitamin D -Sunlight, Eggs, Fish

- **Vitamin B12:** It plays the role as immunomodulator in cellular immunity.

  Sources of Vitamin B12- Meat, liver, fish and dairy products

CERTAIN DO'S AND DON'TS :

Do's	Don'ts
Eat a filling and balanced breakfast like Idli, Dosa, Upma, Poha, Paratha, Sandwiches, Roti sabji to boost you energy at the day's start.	Do not skip your breakfast.
Eat small and frequent meals throughout the day to keep up the energy level.	Do not skip any meal or keep long gaps between meals.
Drink plenty of liquids especially warm water all through the day to keep you body hydrated.	Dehydration can cause lethargy, tiredness and digestive issues.
Eat freshly cooked foods.	Avoid eat street foods or uncovered foods.
Wash hands thoroughly with soap and water before preparing, eating and after handling food.	Do not handle foods if you are sick.
Eat foods that boost your immunity.	Avoid junk food, processed sugars and aerated drinks.
Hydrate yourself with water, fresh juices and soups.	Avoid usage of too much alcohol as they immune system may weaken.
Include salads and fruits that are freshly cut to increase intake of vitamins and minerals for the immune system.	Frozen or packed cut fruits and vegetables should be avoided.
Sleep for a minimum of 7 hours to boost the immune system.	Do not indulge in gadgets before sleeping as it can cause disturbed sleep.

RECIPES TO BOOST IMMUNITY:

Sweet Potato and Carrot Soup:

1. Boil sweet potato and carrot together and puree. Do not strain.
2. In 1 teaspoon coconut oil, add crushed ginger garlic and finely chopped spring onion bubs and sautee.
3. Add the vegetable puree and boil.
4. Add salt and pepper to taste.
5. Adjust the consistency with vegetable stock and sprinkle spring onion leaves.

Star Anise tea:

1. Add 2 star anise to 250ml boiling hot water.
2. Add crushed ginger to it.
3. Add a piece of jaggery and squeeze half a lime juice before drinking.

Imuunity Booster Smoothie:

1. Crush strawberries, Papaya, Kiwi (can add fruits of your choice) in a blender.
2. Add 2 tablespoons fresh yoghurt.
3. Add 1 tsp of powdered seeds (Flaxseeds, Pumpkin seeds and sunflower seeds)
4. Add mint leaves for flavor.

Garlic Tadka Spinach Gravy:

1. Blanch spinach and puree it.
2. In a pan, add coconut oil, 1 star anise, cumin

seeds and and finely chopped spring onion bulbs.

3. Add crushed garlic and ginger and sautee.
4. Add turmeric powder and little dry mixed spice powder.
5. Add the pureed spinach and cook.
6. Add salt to taste. (Can add pulses like boiled channa dal or moong dal)

Rasam:

1. Coarsely grind garlic, back pepper, jeera (1tbsp each).
2. In a pan add 1 teaspoon coconut oil and mustard seeds till it splutters.
3. Add curry leaves and the ground mixture and sautee for a minute.
4. Add turmeric powder, Salt and Asafoetida and sautee.
5. Add 1 tomato puree and cook.
6. Add 2 spoons of tamarind extract and 500ml water and give vigorous boils.
7. Add coriander leaves.

Mix veg Cutlets:

1. Boil vegetables (Potato/Sweet potato, Carrot,Capsicum, beetroot, Spinach, Broccoli, Beans, Green peas).
2. Mash all together with ginger garlic paste and spices like turmeric, black pepper, coriander powder and lime juice salt.
3. Make into cutlet/Pattice shapes and shallow fry on medium flame in coconut oil.

Millet Mix veg Paratha:

1. Mix 50gms each of Jowar (Sorghum), Bajra (Pearl Millet), Ragi (Finger Millet) and Wheat flour.
2. Grate carrot, Beetroot, Mashed and boiled peas, Boiled dal(lentils) and add Chopped onion.
3. Add 1teaspoon mixed seeds(Sunflower, Flax and Pumpkin seeds).
4. Add coriander leaves and spices (turmeric powder, Chilli/Black pepper powder, Coriander powder) and salt.
5. Add 2 tablespoons fresh yogurt and make a dough of all the ingredients.
6. On a pan/Griddle, place the rolled paratha and cook on both sides with coconut oil till golden brown.

Mix Stir fried veg:

1. Add chopped carrots, broccoli, bell peppers, Corn beans, Onions, Spinach in a Wok with little coconu
2. Add black pepper, salt, mixed herbs (Oregano, Ba sautee till cooked.

Symptoms of COVID-19 with Nutrition Implications

NUTRITION MANAGEMENT FOR MILD SYMPTOMS

The symptoms include runny nose, fever, cough, headache and sore throat.

Recommendations

- Adequate fluid intake is important, including minimum 2 liters of water in a day is important.
- Calorie requirement increases because of fever, so its very important to eat nutrient dense meal every small and frequent meals like energy-rich foods, meat, milk, legumes and pulses, fruits and vegetables.
- Supplementation with Vitamin C, zinc, Vitamin A, B6, D, E, iron, Folate and fiber may require if not getting enough from the diet.

- Ensure enough sleep, reduced stress, exercise, avoid intake of alcohol and tobacco products.
- Coughs can be relieved by use of honey, soups, gargling.

Dry Mouth and Sore throat

- Dry mouth can be relieved by use of soothing foods such as warm liquids vegetable soup or chicken soup, warm water, some honey with ginger or soonth.
- Sore throat can be relieved by taking tea, honey, ginger, turmeric.
- Try to include 6-8 glasses of fluid each day.
- Limit intake of refined carbohydrates such as sugar, sweets, cake, soft drinks and sugar sweetened beverages.
- Limit intake of foods containing trans-fats and saturated fats e.g. fat and skin from meat, hydrogenated vegetable oils, shortening, fried foods, and pastries.

A. NUTRITION MANAGEMENT FOR PULMONARY DISEASE

Pulmonary disease includes Mild pneumonia, severe pneumonia, and acute respiratory distress

- If early satiety advise patients to eat small frequent nutrient dense meals
- If anorexia advise to eat preferred nutritious meals or snacks. Increase intake of fruits.

  Vitamins and mineral supplements may improve on appetite and food intake.

- Patients with Weight loss:

  It is important to ensure adequate intake of food from all food groups.

  To prevent muscle wasting it is important eat adequate amount of protein in the diet.

- Fatigue

  Including a source of protein at every meal to sustain energy released from

food.

Limit sweets and sugary food.

Avoid alcohol and caffeine.

Eat small frequent meals

A multiple micronutrient supplement may be considered for patients at risk of vitamin and minerals deficiency or whose intake is inadequate.

As pulmonary disease progresses, other related conditions may interfere with food intake or overall nutrition status.

These include: Abnormal production of sputum

- Increase intake of Fruits and Vegetables like including citrus fruits and leafy vegetables
- Increase intake of warm drinks including clear soups, meaning soups without cream or dairy,
- Some foods may cause increased mucus production if anyone is allergic or intolerant to them, avoid any of these foods if they cause allergic reaction.

Vomiting

- Eat small frequent nutritious meals.
- Eating dry foods and snacks are helpful
- Avoid taking food together with fluids. Take fluids separately.
- Eat food in propped up position and take some time before laying down again.

Anemia

- Including iron rich foods with Vit C rich foods.
- Supplementation may be needed depending on severity and cause of anemia.

Fluid retention

- Sodium and fluid restriction are required for some patients having fluid retention. Sometimes increased dietary intake of potassium may be required, depending on the diuretics used.
- Use of calorically dense enteral feedings may help the meet energy needs.

Enteral feeding

- Patients receiving inadequate oxygen may require enteral feeding.
- Intubated patients usually require enteral tube feeding or parenteral feeding.
- The gastrointestinal route is preferred, although aspiration and bacterial overgrowth are concerns.
- Feeding procedures that minimize aspiration include the use of a continuous method of feeding rather than large bolus feedings.

17 Physical and Pulmonary Rehabilitation

Introduction

Early evaluation and rehabilitation interventions are the effective way to avoid complications, disease deterioration and reduce the risk of severe post-recovery disability for individuals with COVID-19. The physiotherapists have a vital role in facilitating more energy-conserving techniques of breathing and mobilisation. Physiotherapy not only promotes an enhancement in the oxygenation required for patients who have low oxygenation due to breathing problems, but also boosts their immune system which will in turn help them fight against the disease.

The patients with COVID-19 require rehabilitation that helps to improve respiratory function, reduce mechanical ventilation (MV) time, reduce the risk of complications, length of hospital stay, readmission risks and to help functional recovery and improve patient quality of life (QoL) during the acute, sub-acute and long-term phases of the disease.

To determine the indications for referral to physiotherapy in patients with confirmed or suspected COVID-19:

- Physiotherapy interventions are not indicated for airway clearance in patients who Mild symptoms without significant respiratory compromise, e.g., fever, dry cough, no chest X-ray changes.
- Physiotherapy interventions are not indicated for airway clearance in patients with nonproductive cough or patient coughing and able to clear secretions independently.

- Physiotherapy referral for airway clearance in patients with mild symptoms and/or pneumonia along with coexisting respiratory or neuromuscular comorbidity and current or anticipated difficulties with secretion clearance.

- Physiotherapy referral for airway clearance in patients with mild symptoms and/or pneumonia and with the evidence of exudative consolidation having difficulty to clear or inability to clear secretions independently. E.g. weak, ineffective, and moist sounding cough, tactile fremitus on chest wall, moist/wet, sounding voice, audible transmitted sounds

- Physiotherapy may be indicated for airway clearance; if there is presence of weak cough, productive, and/or evidence of pneumonia on imaging and/or secretion retention; in patients with severe symptoms that are suggestive of pneumonia/lower respiratory tract infection. E.g., increasing oxygen requirements, fever, difficulty breathing, frequent, severe or productive coughing episodes, chest X-ray/CT/lung ultrasound changes consistent with consolidation.

- The patients with severe COVID-19 and critically ill patients should not be recommended early respiratory rehabilitation if their condition remains unstabilized or progressively deteriorates.

Aim of rehabilitation:

- Aid in airway clearance
- Relieve dyspnea
- Reduce work of breathing
- Improve lung compliance
- Improve respiratory endurance
- Improve muscular strength and endurance
- Improve general mobilisation
- Reduce fatigability
- Reduce complications

A. Screening & Rehabilitation for patients with mild COVID-19

<u>Symptoms</u>

1. Fever
2. Dry cough
3. Fatigue
4. No chest x-ray changes

5. Without significant respiratory compromise
6. Headache
7. Bodyache

Rehabilitation:

A) Activity recommendations

1. Exercise intensity: [5]

a) Borg dyspnea score of 3 (total score:10 points) (Figure:1 Borg scale)

RPE SCALE	
1	Nothing
2	Very Easy
3	Easy
4	Comfortable
5	Somewhat Difficult
6	Difficult
7	Hard
8	Very Hard
9	Extremely Hard
10	Maximal/Exhaustion

b) No complaints of fatigue should be present on 2nd day

2. Exercise frequency: [5]

a) Two times a day

b) 15 to 45 min/session of duration

c) 1 hour after meals

3. Type of exercise:

a) Breathing exercises such as pursed lip breathing (Figure 2), deep breathing exercises in lying & sitting upto 8-10 breaths / thrice a day (Figure 3 & 3b), diaphragmatic breathing exercises (Figure 4), apical & lateral costal

breathing exercises upto 8-10 breaths / twice a day (Fig 5) and spirometry exercises upto 8-10 breaths / thrice a day (Fig 6).

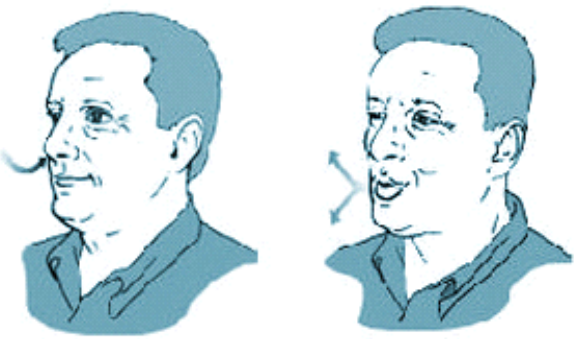


Fig 2 - Pursed lip breathing

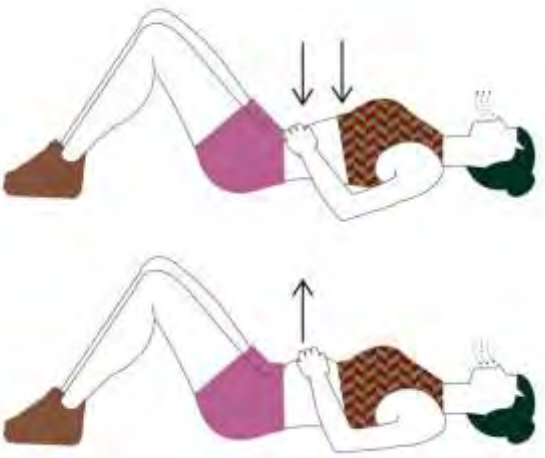


Fig 3a, 3b1-3b2- deep breathing exercises in lying & sitting diaphragmatic breathing exercises (Figure 4

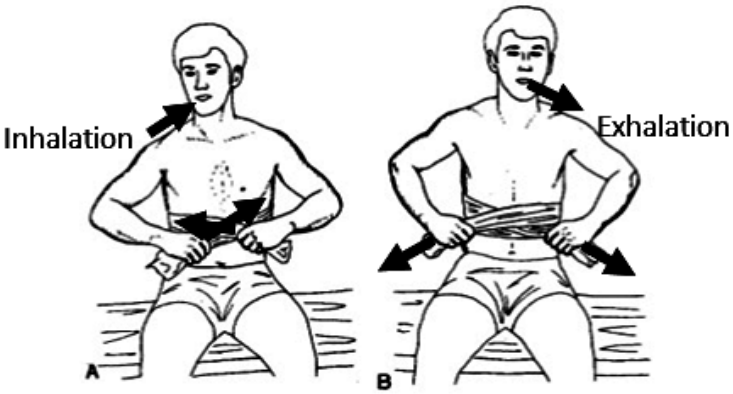


Fig 5- apical & lateral costal breathing exercises

Fig 6a and 6b - Spirometry Exercises

b) Airway clearance techniques such as active cycle of breathing technique & huffing (Fig 7),percussion & vibrations (Fig 8) and positive expiratory pressure therapy (PEP)

Fig 7 - Active Cycle of Breathing Technique & Huffing

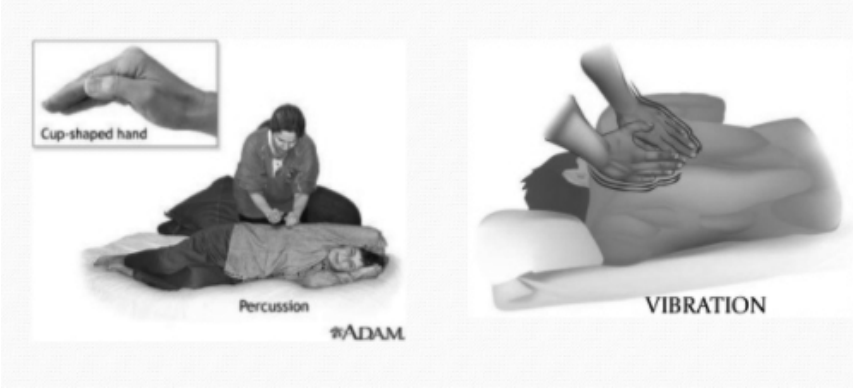


Fig 8 - Percussion & Vibrations

c) Postural Drainage to assist in mobilizing the secretions from peripheral to central airways (Fig 9).

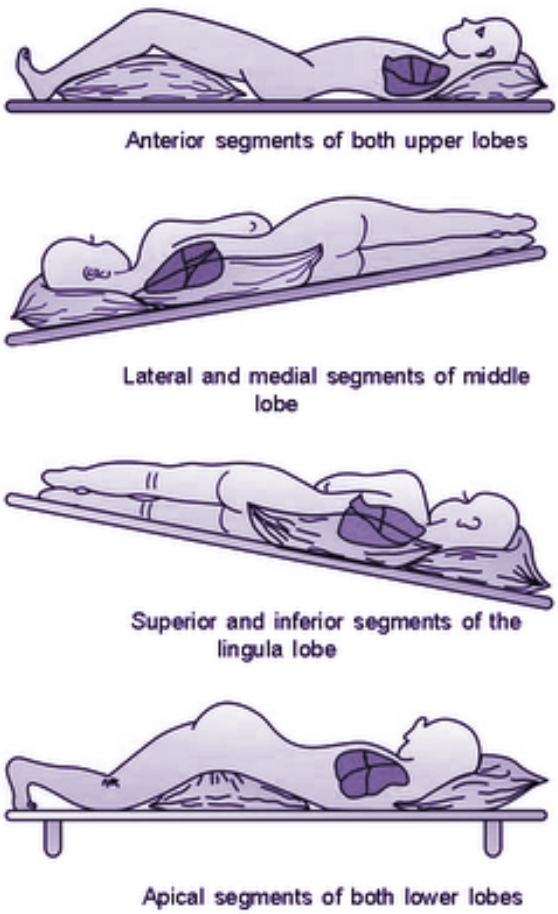
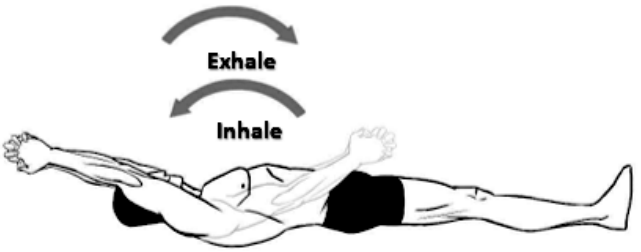


Fig 9 - Postural Drainage

d) Posture management

e) Activities to improve chest expansion along with upper extremity exercises in supine, sitting & standing (Fig 10a,10b1 & 10b2,10c)



10a

10b1

10b2

10 c1, 10c2

Chest expansion along with upper extremity exercises in supine, sitting & standing (fig 10a,10b1 & 10b2,10c)

f) Yoga to improve breathing: Anulom –Vilom: 'Pranayam' a routine practice in 'Yoga' it is strongly recommended to practice this breathing technique at least two to three times a day. (Fig 11)

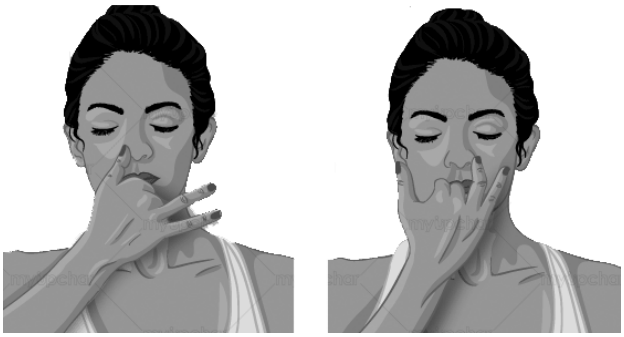


Fig 11 - Anulom –Vilom

Below are the instructions for how to do it.

Starting position: Sitting in the chair upright keeping your shoulder relaxed or any other position comfortable to you

Breathing technique: begin from the left then close the right nostril with the right thumb and inhale slowly to fill up the lungs. Now, exhale slowly from the right nostril. Repeat by inhaling through left nostril and exhaling through right nostril. Practice this technique for 20 -30 breaths / twice a day

B) Patient education

a) Regular rest
b) Sufficient sleep
c) Balanced diet
d) Videos and booklets should be used to help patients understand the disease and treatment process
e) Advised to stop smoking.

B. Screening & Rehabilitation for patients with moderate COVID-19

<u>Symptoms:</u>

1. Fever
2. Cough
3. Dyspnea
4. Fatigue

5. Muscle ache/ myalgia
6. Bodyache
7. Decrease in muscle strength due to prolonged bed rest
8. Poor expulsion of sputum due to decreased muscle strength
9. Increased risk of deep vein thrombosis

Rehabilitation:

The objective is to maintain the existing physical status so the exercise intensity should not be too high.

The following points to be considered while screening to determine if respiratory rehabilitation can be initiated:

a) Duration from disease onset to dyspnea
b) Assessment of blood oxygen saturation (SpO2)

A) Physical activity and exercise recommendations:

(I) Intensity:

- Between rest and light exercise (1.0 metabolic equivalents [METs] to <3.0 METs)

(ii) Frequency:

- Two times a day
- 1 hour after meal

(iii) Duration: (based on the patient's physical status)

- 15 to 45 min each session
- Intermittent exercise or with an appropriate rest intervals for patients who are prone to fatigue or are physically weak

(iv) Type of exercise:

- Breathing exercises such as pursed lip breathing, deep breathing exercises, diaphragmatic breathing exercises, apical & lateral costal breathing exercises and spirometry exercises.

I) Airway clearance:

(i) To help sputum expectoration, deep breathing exercises can be used

(ii) To avoid virus transmission, a sealed plastic bag should be used when coughing

II) Breathing control:

(I) Positioning:

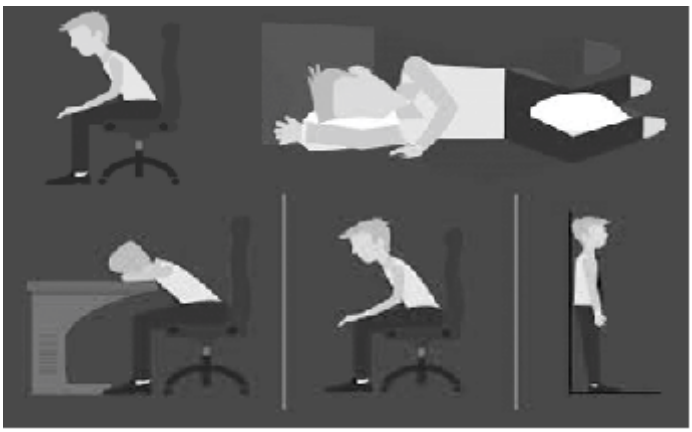


Fig 12

a) An upright sitting position must be adopted

b) A semi-sitting position or a leaning forward position must be adopted in patients with shortness of breath (Fig 12)

(ii) Maneuvers:

a) The accessory muscles of the shoulders and neck must be relaxed during training.

b) The instructions by therapists, should be loud & clear, would be slowly inhale through the nose & slowly exhale through the mouth while the patient places the hand on diaphragm

c) The therapist's attention must be at the expansion of the lower chest along with abdominal flaring.

- Exercises such as ankle toe movements (Fig 13), active lower extremity exercises in lying (heel slides) (Fig 14) or sitting and standing (knee flexion & extension & hip-knee flexion & extension) (Fig 15a & 15b) to prevent thrombosis

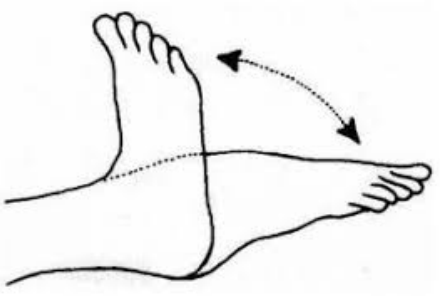


Fig 13 - Ankle Toe Movement

Fig 14 - Lower extremity exercises in lying (heel slides)

Fig 15a1, 15a2, 15b - (Knee flexion & extension & hip-knee flexion & extension)

- Early mobilisation is encouraged. Actively mobilise the patient early in the course of illness when safe to do so.
- Activities such as sitting out of bed, simple physical exercises such as knee flexion & extension, thoracic expansion exercises in sitting & standing using upper extremities co-ordinated with breathing are recommended for the patients to be functional.
- Activities like walking around, stair climbing with proper monitoring of vitals including heart rate, respiratory rate & SPO2.

- An individual training program is developed depending on the patient's endurance.

Exercise termination criteria

When one of the following conditions develops during respiratory rehabilitation, it is recommended to immediately discontinue and assistance should be sought from physicians and nurses.

- Dyspnea index: Borg dyspnea score >3 (total score: 10 points)
- Chest tightness,
- Dizziness
- Shortness of breath
- Headache
- Blurred vision
- Heart palpitations

- Profuse sweating
- Balance disorder

C. Screening & Rehabilitation for patients with severe COVID-19

The respiratory rehabilitation plays an important role in the three groups of COVID-19 patients:

1) Acute phase, patients with critical respiratory impairment (first aid, emergency department, ICU, step down unit)

2) Acute phase, patients with severe respiratory impairment (internal medicine, respiratory, infectious disease, or other wards); and

3) Post-acute phase (other units, intermediate care facilities, subacute wards).

Symptoms:

1. Hypoxemia
2. Acute Respiratory distress syndrome (ARDS)
3. Septic shock
4. Metabolic acidosis
5. Chest CT scans have revealed distinct patterns of pulmonary involvement in COVID-19 patients:

- An overperfused ground-glass phenotype, multifocal, with centrilobular nodules, patchy consolidation,and intra-bronchial air bronchogram
- Dilatation and congestion of septal capillaries that is followed by exudation into the alveolar space with interstitial edema
- Vascular exudation in the interstitium with consolidations filled by air bronchogram
- Fibrous exudation with multiple consolidations
- Thickening of bronchial walls, the interlobular septum, and patchy consolidations

6. Patients put on mechanical ventilation are under deep sedation and receive analgesia tend to completely lose spontaneous breathing and have no or weak response to stimuli, and the incidence of delirium in such patients is high

Indications of Respiratory rehabilitation only when all of the following criteria are met:

A) Respiratory system:

(i) Fraction of inspired oxygen, if it is less than or equal to 0.6

(ii) SpO2 ≥90%

(iii) Respiratory rate- 40 breaths/min (bpm)

(iv) Positive end expiratory pressure- 10 cmH2O (1 cmH2O = 0.098 kPa)

(v) Absence of ventilator resistance

(vi) Absence of unsafe hidden airway problems

B) Cardiovascular system:

(i) Systolic blood pressure ≥90 and 180 mmHg

(ii) Mean arterial pressure (MAP) ≥65 and 110 mmHg

(iii) Heart rate ≥40 and 120 beats/min

(iv) Absence of new arrhythmia or myocardial ischemia

(v) Absence of shock with lactic acid level ≥4 mmol/L

(vi) Absence of new unstable deep vein thrombosis and pulmonary embolism

(vii) Absence of suspected aortic stenosis

C) Nervous system:

(i) Richmond Agitation-Sedation Scale score: 2 to +2

(ii) Intracranial pressure<20cmH2O

D) Others:

(i) Absence of spinal fractures and unstable limb

(ii) Absence of severe underlying hepatic/renal disease or new progressively worsening hepatic/renal impairment

(iii) Absence of active hemorrhage

(iv) Temperature 38.5°C.

Rehabilitation

(1) Positioning management:

To improve oxygenation positioning is important: the best position for a patient is in a semi sitting or sitting position while moving from the reclined position. Variation in positions can be very useful in case of pressure sores. The positions should be resolved in fixed movements to reduce, relax the muscles and promote the ventilation / perfusion ratio.

- Anti-gravity posture simulation is gradually increased until the patient can maintain an upright position such as raising the head of the bed by 60°.
- To prevent head hyperextension, the lower edge of the pillow is placed on one-third of the scapula.
- To relax the lower limbs and abdomen, a pillow is placed below the popliteal fossa to relax the lower limbs and abdomen.
- Duration: 30- min sessions
- Frequency: three sessions each day

COVID awake repositioning prone protocol (CARP) (adopted from Intensive Care Society

Guidelines 2020):

In non-intubated patients or patients on NIV or high-flow nasal oxygen (HFNO) therapy, the "COVID awake repositioning proning protocol" (CARP) has to be implemented on suitable patients on screening for indications and SpO2 monitored with pulse oximeter

If the criteria for proning is fulfilled by the patient, ask the patient to switch positions as follows. Oxygen saturations are monitored 15 min after each position change to ensure oxygen saturation has not decreased. Continue to monitor oxygen saturations

- 30 min to 2 hour lying fully prone (bed flat)

- 30 min to 2 hour lying on right side (bed flat)
- 30 min to 2hour sitting up (30–600) by adjusting head of the bed
- 30 min to 2hour lying on left side (bed flat)
- 30 min to 2 hour lying prone again

Continue to repeat the cycle

To reduce shortness of breath:

- Breath control - Semi-reclined position is recommended. The patient is advised to relax the inspiratory muscles, in particular those of the arms and neck. At this point the patient begins to breathe in through the nose (warms and hydrates the air). The patient performs a moderate relaxation and widens at the expiration with the establishment of adequate airways (lower thoracic breathing and stomach). Breathing should be calm (shallow, slow).
- It is concluded with the alleged relaxing lip of the lips. This method can be added for normal breathing while the patient rest and keeps this movement in mind. It serves to slightly fix the lips while you exhale.

(2) Early mobilization:

To prevent tubing detachment, vital signs should be monitored during the entire process attention should be paid during the entire activity

(I) Intensity:

- Lower resistance
- Minimal duration
- Patients only need to complete the movements

(ii) Duration:

- The session should not exceed 30 min at a time
- No exacerbation of fatigue

(iii) Type of exercise:

- Regular turn over and movement on the bed
- Sitting up on bed
- Moving from the bed to chair
- Sitting on the chair
- Standing up
- Stepping should be carried out step by step
- Active/passive exercise training is performed within the full range of motion (ROM)
- Treatments such as bedside lower limb passive exercise bicycle, passive joint movement and stretch exercise, and neuromuscular electrical stimulation for patients receiving sedatives or patients with loss of consciousness, cognitive dysfunction, or with limited physiological conditions,

C) Respiratory management:

- Lung recruitment
- Sputum expulsion
- No long periods of patient contact by therapist
- Management should not trigger severe cough and increase the work of breathing
- High-frequency chest wall oscillation and oscillatory positive expiratory pressure (OPEP)

Exercise termination criteria

A) Respiratory system:

(i) SpO2 <90% or decrease by>4% from baseline

(ii) Respiratory rate >40 bpm

(iii) Ventilator resistance

(iv) Artificial airway dislodgement or migration

B) Cardiovascular system:

(i) Systolic blood pressure <90 or >180 mmHg

(ii) MAP <65 or>110 mmHg, or >20% change compared with baseline

(iii) Heart rate <40 or >120 beats/min

(iv) New arrhythmia and myocardial ischemia

C) Nervous system:

(i) Loss of consciousness

(ii) Irritability

D) Others:

(i) Discontinuation of any treatment or removal of monitoring tube connected to the patient

(ii) Heart palpitations

iii) Exacerbation of dyspnea

iv) Shortness of breath

v) intolerable fatigue

vi) fall in vitals of patient

Rehabilitation in outpatient patients with post-COVID-19:

The following treatment goals can be considered:

- Improving general fitness
- Increase mobility: independent transfers, independent walking, climbing stairs
- Prevent loss of function: contractures, pulmonary complications and decubitus

- Respiratory force and adequate coughing techniques
- ADL independence
- Improve arm/hand function
- Insight/coping due to reduced energy
- Understanding compensation strategies
- Healthy nutritional status
- The consequences of prolonged ICU admission may have on patients. Hence, rehabilitation is important for these patients

Rehabilitation of patients with COVID-19 who encounter psychological disorders

Symptoms:

1. Anger
2. Fear
3. Anxiety
4. Depression
5. Insomnia
6. Aggression
7. Loneliness
8. Lack of Cooperation
9. Will be uncooperative due to fear of the disease

All these above symptoms can lead to dyspnea, increased heart rate, elevated blood glucose levels, hyperlactic acidemia, lower blood pressure & thus affects the effectiveness of rehabilitation which further needs to be addressed.

Psychological counselling may help these patients. An interactive communication, stress management, and personalized care is provided by clinical psychologists.

Telerehabilitation:

Asymptomatic or mild covid patients are quarantined at home. Aim is to stop the spread of COVID-19 and to remain confined to homes, with the exception of essential basic services. Home isolation implies a notable physical

deconditioning. The positive experiences have been reported in Telerehabilitation methods.

- Breathing exercises such as spirometry exercises, pursed lip breathing, thoracic expansion exercises.
- General mobility exercises such as spot marching, slow lunges, walking & stair climbing & descending.

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18 Psychological Counselling for COVID-19 Patients

Introduction

Addressing mental health and psychosocial aspects of Covid-19 outbreak is key to psychological wellbeing in patients in emergency settings.The global definition of the composite term 'mental health and psychosocial support' (MHPSS) is used in the Inter Agency Standing Committee (IASC) Guidelines for MHPSS in Emergency Settings to describe 'any type of local or outside support that aims to protect or promote psychosocial well-being and/or prevent or treat mental health condition'. The global humanitarian system uses the term MHPSS to unite a broad range of actors responding to emergencies such as the COVID-19 outbreak, including those working with biological approaches and sociocultural approaches in health, social, education and community settings, as well as to 'underscore the need for diverse, complementary approaches in providing appropriate support'. IASC Guidelines for Mental health and psychosocial support (MHPSS) in Emergency Settings recommends that multiple levels of interventions be integrated within outbreak response activities. These levels align with a spectrum of mental health and psychosocial needs and are represented in a pyramid of interventions ranging from embedding social and cultural considerations in basic services, to providing specialised services for individuals with more severe conditions. Core principles include: do no harm, promote human rights and equality, use participatory approaches, build on existing resources and capacities, adopt multi-layered interventions and work with integrated support systems. Checklists for using the guidelines have been produced by the IASC Reference Group.

IASC Reference Group on MHPSS in Emergency Settings.

In any epidemic, it is common for individuals to feel stressed and worried. Common responses of people a ected might include fear, anxiety, worry, stressors, unrealistic reactions etc. As a mental health professional, one can target specific problems or areas and focus interventions on the basis of requirement, which could be unique to each individual patient.

Issues Commonly Faced By Patients And Their Caretakers

It's common in an epidemic for individuals to feel stressed and worried. Responses of people affected both directly and indirectly might include:

Fear of falling ill and death.Avoiding approaching health facilities due to fear of becoming infected while in care. Fear of losing livelihoods, not being able to work during isolation, and of being dismissed from work.Fear of being socially excluded/placed in quarantine because of being associated with the disease (Eg: discrimination against people who are from, or perceived to be from, a ected areas).Feeling powerless in protecting loved ones and fear of losing loved ones.Fear of being separated from loved ones and caregivers due to quarantine regime.Refusing to take to care for unaccompanied or separated minors, people with disabilities or the elderly due to fear of infection, because parents or caregivers have been taken into quarantine.Feelings of helplessness,

boredom, loneliness and depression due to being isolated. Emergencies are stressful, but certain stressors are specific to COVID-19 outbreak affect the population.

Major Stressors include:

Risk of being infected and infecting others, especially if the transmission mode of COVID-19 is not 100% clear. Common symptoms of other health problems (e.g. a fever) can be mistaken for COVID-19 and lead to fear of being infected. Caregivers may feel increasingly worried for their children being at home alone (due to school closures) without appropriate care and support. School closures may have a differential effect on women, who provide most of the informal care within families, with the consequences of limiting their work and economic opportunities.Risk deterioration of physical and mental health of vulnerable individuals, for example older adults and people with disabilities, if caregivers are placed in quarantine if other care and support is not in place.Some of these fears and reactions spring from realistic stressors or dangers, but many reactions and behaviours are also born out of lack of knowledge, rumours and misinformation.

Social stigma and discrimination can be associated with COVID-19, including towards persons who have been infected, their family members and health care and other frontline workers. Steps must be taken to address stigma and discrimination at all phases of the COVID-19 emergency response. Care should be taken to promote the integration of people who have been affected by COVID-19 without over-targeting.

Internvention
(What can be done to improve the mental health of patients and caregivers)

Stressors of COVID-19 can be specific to individuals, and interventions should be catered according to individual needs. Common areas that need to be focused on, are as follows:

- Fear

Multiple reasons of Fear, such as falling sick and dying. Avoiding going to health facilities due to fear of becoming infected while in their care. Fear of losing income, not being able to work during isolation, and of being relieved from work.Fear of being socially excluded/ placed in quarantine because of being associated with the disease.Feeling powerless in protecting loved ones

and fear of losing loved ones because of the virus.Fear of being separated from loved ones due to quarantine. Refusal to care for unaccompanied or separated minors, people with disabilities or the elderly due to fear of infection, because parents or caregivers have been taken into quarantine.Feelings of helplessness, boredom, loneliness and depression due to social isolation. Some may develop irrelevant or illogical fears, addressing the stressors and dealing with them rationally will help lower anxiety.

Patients should also be encouraged to adopt Metacognition.

- Psychosocial Support

Psychosocial interventions refer to strategies that target excessive, uncontrollable stress, concern and persistent excessive arousal. Mental health professionals like psychologists, psychiatrists and psychiatric social workers help the patients and community to understand the potential impact of the virus and help patients, societies and families deal with the potential threat on physical and mental health. Several Psychological assistance services, including telephone, internet and application-based counselling or intervention, have been widely deployed by local and national mental health institutions in a response to the COVID-19 outbreak as the availability of transparent and timely information is important for the emotional restraint of family members and for keeping the general population calm. Unconventional methods can sometime help patients get through the situation, as to provide them with support not as a mental health professional but as a friend or a companion. Giving patients plenty of opportunities for cathartic release and emotional expression.

Understanding and addressing mental health and psychosocial considerations will be key to stopping transmission and preventing the risk of long-term repercussion on the population's wellbeing and capacity to cope with adversity .

- Positive Psychology

Positive psychology focuses on the positive events and influences in life, such as:

- Positive experiences like happiness, joy, inspiration, and love.
- Positive states and traits like gratitude, resilience and compassion.
- Positive institutions applying positive principles within entire organisations and institutions.

As a field, positive psychology spends much of its time thinking about topics like character strengths, optimism, life satisfaction, wellbeing, gratitude, compassion, self esteem, self confidence, hope and elevation.On a more positive note, some people may have positive experiences, such as pride about being able to find ways of coping and resilience. Faced with disaster, community members often show great altruism and cooperation, and people may experience great satisfaction from helping others.

- Positive Environment

It includes the integration of MHPSS approaches and activities within community strategies, community outreach, case identification and contact tracing, as well as activities at health facilities and quarantine sites.Strong emphasis needs to be placed on the strength and resourcefulness of communities rather than weaknesses and vulnerabilities. Healthcare workers must seek to create safe and protected environments for care and make use of existing resources and strengths. Individual worker and the collective team should ensure that all actions promote protection and wellbeing. Key psychosocial principles, including hope, safety, calm, social connectedness and self- and community efficacy, should be embedded across every intervention.

- Specific care interventions for Specific/High risk groups

Older adults, especially in isolation and those with cognitive decline/dementia, may become more anxious, angry, stressed, agitated, withdrawing, overly suspicious during the outbreak/while in quarantine. Provide emotional support through informal networks (families) and mental health professionals. Share simple facts about what is going on and give clear information about how to reduce risk of infection in words older people with/ without cognitive impairment can understand. Repeat the information whenever necessary.Older adults are particularly vulnerable to COVID-19 given their limited information sources, weaker immune systems, and the higher COVID-19mortality rate found in the older population. Older people with mild cognitive impairment or early stages of dementia need to be informed of what is happening within their capacity and provided support to ease their anxiety and stress. For people at moderate and late stages of dementia, their medical and daily living needs need to be met during the quarantine time specific attention to high-risk groups, i.e. older people who live alone/without close relatives; who have low socioeconomic status and/or co-morbid health conditions such as cognitive decline/dementia or other mental health conditions, people with disabilities

or other forms of disorders, Vulnerable groups (Eg: women with history of abuse, children or any other individuals with a history of abuse).

Encourage active listening and an understanding attitude with the children. Children may respond to a difficult/unsettling situation in di erent ways: clinging to caregivers, feeling anxious, withdrawing, feeling angry or agitated, having nightmares, bedwetting, frequent mood changes, etc. Children usually feel relieved if they are able to express and communicate their disturbing feelings in a safe and supportive environment. Every child has his/her own way to express emotions. Sometimes engaging in a creative activity, such as playing and drawing can facilitate this process. Help children find positive ways to express disturbing feelings such as anger, fear and sadness.Encourage an increased sensitive and caring environment around the child. Children need adults' love and often more dedicated attention during di cult times.Children often take their emotional cues from the important adults in their lives, so how adults respond to the crisis is very important. It's important that adults manage their own emotions well and remain calm, listen to children's concerns and speak kindly to them and reassure them. If appropriate and depending on the age, encourage parents/caregivers to hug their children and repeat that they love them and are proud of them. This will make them feel better and safer. If possible, make opportunities for children to play and relax. Keep children close to their parents and family, if considered safe for the child, and avoid separating children and their caregivers as much as possible. If a child needs to be separated from his/her primary caregiver, ensure that appropriate alternative care is provided and that a social worker, or equivalent, will regularly follow up on the child. If children are separated from their caregivers, ensure regular and frequent contact (e.g. via phone, video calls) and re- assurance. Ensure all child protection and safeguarding measures are addressed.

- Holistic approach towards Health

Engaging in healthy activities that they enjoy and find relaxing. Exercising regularly, keeping regular sleep routines and eating healthy food. Keeping things in perspective. To try and to keep your their personal daily routines or create new routines if circumstances change as much as possible. Indulging in Yoga, meditation, community

based activities, art etc.A constant stream of news reports about the outbreak can cause patients to feel anxious or distressed. Remind them to Seek information, updates and practical guidance at specific times during the day

from health professionals or appropriate websites and avoid listening to rumours that make them feel uncomfortable.

Encouraging patients to be connected with their family and maintaining social networks.During times of stress, encouraging them to pay attention to their own needs and feelings. Training all the medical frontline workers including non-health workers in quarantine sites, on essential psychosocial care principles, psychological first aid and how to make referrals when needed, is very necessary. COVID-19 treatment and isolation/ quarantine sites should include trained staff.

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19 Yoga

Yoga is a multicomponent, mind–body medicine, comprising low intensity exercises, breath control techniques, relaxation, mindfulness and meditation. Yoga is cost neutral, easy-to-learn and practice, and largely a safe form of exercise. Yoga is welcomed world over for its health promoting and wellness creating aspects. Research over three decades both at this university and elsewhere has shown the efficacy of yoga practices including meditation in establishing homeostasis in noncommunicable diseases by reducing stress levels and promoting healthy lifestyle.

Boosts Immunity

Immunity of the host is an essential requisite to facilitate the eradication of infections. Disturbed immune systems seen as lymphopenia and elevated C-reactive protein levels are recognized to be the characteristic features in severely affected cases of COVID-19 infection. A systematic special tailor-made asana practices, dedicated pranayamas, meditation, and mantras can provide a broad-spectrum immune build up in the body so that viral infection could be averted and/or its virulence reduced.

Improves Oxygenation

The upper respiratory tract being the portal of entry for the SARS-CoV-2 virus infection, the health of the respiratory system is very important in preventing fatality. There are several reports of clinical trials that suggest an overall effect of yoga training toward improved pulmonary function in patients with chronic obstructive pulmonary disease.

Relieves Stress

Rising numbers of COVID-19 cases and deaths possibly raise stress and anxiety, while loneliness and depressive feelings are likely due to mandatory social distancing measures. All yoga practices utilize deep relaxation which could release all tensions and stresses to prevent immune suppression that would otherwise have weakened the responses to the onslaught of infectious bacteria and viruses.

Several yoga techniques are available to develop mastery over the mind by enhancing the willpower that keeps the immune system strong. These include asana, pranayama, meditation with or without using Mantras, and detoxification through kriyas.

Pranayam:

1. ANULOM-VILOM

lose your eyes and sit in Padmasana. Use the right thumb to close the right nostril. Inhale slowly through the left nostril, taking in as much air as you can to fill your lungs. Remove the thumb from your right nostril and exhale. While exhaling, use the middle finger to close your left nostril and inhale with our right nostril. Remove the thumb from the right nostril and exhale.

Reps Perform for 2-5 minutes

Benefits: It helps normalise blood pressure, aids in blood purification, reduced risk of heart disease and can also improve sight.

2. BHRAMARI

Close your ears with your thumbs and place your index fingers on the temple. Close eyes with the other three fingers. Gently inhale through the nose and hold for a few seconds. Keeping the mouth closed, exhale by making a humming sound.

Repeat 5 times

Benefits: It can calm your mind down instantly and is one of the best breathing exercises to distress as it rids the mind of frustration, anxiety, anger or agitation.

3. UJJAYI PRANAYAMA

Begin by inhaling and exhaling naturally. Bend down your head, blocking the free flow of air and inhale as long as you can, making a sound from your throat. Hold for 2-5 seconds. Close your right nostril with your right thumb while exhaling and breathe out through the left nostril.

Repeat 10-12 times in as much time you need

Benefits: The sound vibrations that are a part of this pranayama sharpen the focus of your mind can help cure thyroid and reduce snoring.

4. KAPALBHATI

This breathing technique involves passive inhalation and active exhalation. So inhale normally, breathing in as much air as you can, and exhale forcefully. Try and pull your stomach muscles as closely as you can towards the backbone during exhalation.

Perform for 2-5 minutes

Benefits: This can improve the functioning of all abdominal organs, reduces belly fat, leads to quick weight loss and balances sugar levels in your body.

5. BHASTRIKA

Take a deep breath in, inhaling as much air as you can, and expand your stomach. Exhale the air out with force and try and pull your navel in towards the backbone.

Repeat for 1-2 minutes and rest for a while afterwards

Benefits: Perform this breathing technique to strengthen your lungs, burn excess fat, improve physical and mental ability and clear the windpipe.

Yogasana:

1.Shalabhasana- Locust Pose

- Lie flat on your stomach
- Arms can be stretched out ahead
- Keep your knees straight and feet together
- Inhale and lift your legs and arms up together
- Lift your head up raising your chest off the floor as much as possible
- Hold the posture for 10 seconds

2. Tadasana- Mountain Pose

- Stand with your feet together
- Keep your back straight
- Bring your palms together and interlock them
- Inhale and lift your stretch your arms up, palms facing outward
- Look up and gently drop your head back on your shoulders
- Hold for 5-10 seconds. Repeat 1-2 times

3. Krupa Chaturanga Dandasana- Four-Limbed Staff Pose on Elbows

- Start on all fours, ensuring palms are under the shoulders and knees below hips
- Lift your knees off the ground and align your pelvis with your shoulders for Plank Pose
- Slowly drop your elbows on your mat one by one
- Align your elbows with your shoulders
- Engage your core

4.Vrikshasana- Tree pose

It replicates the steady stance of a tree.

- Place your right foot high up on your left thigh.
- The sole of the foot should be flat and placed firmly. Keep your left leg straight and find your balance.
- While inhaling, raise your arms over your head and bring your palms together. Ensure that your spine is straight and take a few deep breaths.
- Slowly exhale, bring your hands down and release your right leg.
- Back in the standing position repeat the same with the other leg.

5.Bhujangasana - Cobra pose

- Lie on your stomach with your feet together and toes flat.
- Place your hands downwards below your shoulders on the mat, lift your

waist and raise your head while inhaling in.

- Pull your torso back with the support of your hands. Keep your elbows straight and make sure you put equal pressure on both palms.
- Tilt your head back and make sure your shoulders are away from your ears. Exhale while coming back to the ground

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Section E

Medicines

20 AntiVirals

1. Hydroxychloroquine (HCQ)

Chloroquine and Hydroxychloroquine (HCQ) are both 4-aminoquinolones that are used extensively in the treatment of malaria and are also utilized for their anti-inflammatory properties in autoimmune disease. They also possess antiviral activity. HCQ is used in COVID-19 because it is safer and has less side effects

Mechanism of Action

One of the earliest studies performed to evaluate the possible effectiveness of pre-approved drugs, was a study that showed the in vitro activity of chloroquine against SARS-CoV-2 virus. HCQ is a derivative of chloroquine and is less toxic. Also, it has shown better anti SARS-CoV-2 activity in vitro. Their antiviral action is mediated through increase in the endosomal pH. This prevents viral entry to the cell since endocytosis is pH dependent. These drugs also interfere with the glycosylation of cellular receptors of SARS-CoV so that it cannot bind to the angiotensin-converting enzyme 2 (ACE2) receptors that are expressed mainly in the lung, heart, kidney and intestine. They also inhibit quinone reductase-2 that is involved in sialic acid biosynthesis. Sialic acid is an acidic monosaccharide of cell transmembrane proteins required for ligand recognition. They inhibit viral post-translational modifications and replication. HCQ thus functions as a broad antiviral agent at both entry and at post-entry stages of SARS-CoV-2 infection. Besides, when administered orally it gets widely distributed in the whole body including the lungs. The immune-modulating activity may further enhance it's antiviral effect in the body.

Published results in COVID-19

A study including 100 COVID-19 patients showed that chloroquine administration reduced symptom duration with evidence of radiological improvement when compared to the control group. Combination of Azithromycin and HCQ has shown to significantly reduce the viral load in SARS-CoV-2 infections as compared to controls. This suggests a synergistic effect of azithromycin with HCQ. However, due to risk of QT prolongation, ECG monitoring is recommended when using this drug combination. Please note that co-administration of Remdesivir with HCQ or Chloroquine is to be avoided. A recent meta-analysis has also demonstrated that patients that had received HCQ were less likely to show radiological progression than patients receiving standard treatment.

Indication

i. Prophylaxis in COVID-19 contacts, family members and healthcare workers, ii. Treatment in COVID-19 suspects, asymptomatic, mild & moderate COVID-19 positive patients

Contraindication

I. Abnormal ECG, ii. Prolonged QT interval >480 msec iii.cardiac arrhythmias, iv. History of IHD, v. unexplained syncope vi.Retinopathy, vii. Allergic/hypersensitive to hydroxychloroquine or chloroquine

Side effects

i. Headache, ii. Nausea, iii. Vomiting, iv. Dizziness, v. Stomach pain or diarrhea, vi. Feeling tired or weak, vii. Change in color of skin, viii. Blurring of vision due to disturbance of accommodation; reversible and dose-dependent, ix. Abnormal liver function tests, x. Skin rash, xi. Pruritus, xii. Sensory-motor disorders, xiii. Hemolytic anemia in patients with G6PD deficiency

Dose

Prophylaxis for Healthcare workers

Tab HCQ 400 mg po twice a day on day 1 followed by 400mg po once a week for 7 weeks. (with meal)

Prophylaxis for COVID-19 contacts and family members

Tab HCQ 400 mg po twice a day on day 1 followed by 400mg po once a week for 3 weeks. (with meal)

Treatment in COVID-19 suspects, asymptomatic, mild & moderate covid positive patients

Adults : Tab HCQ 400 mg po BD on Day 1 followed by Tab HCQ 200 mg po BD for 4 days

Children and adolescents: 6.5 mg/kg q12h on day 1 (maximum initial dose = 400 mg q12h), followed by 3.25 mg/kg q12h on days 2 - 5 (maximum dose = 200 mg q12h)

2. Lopinavir-Ritonavir

It is a combination of the HIV protease inhibitors, lopinavir and ritonavir.

Mechanism of Action

Lopinavir acts against the viral 3CL protease activity and results in production of immature, non-infectious viral particles. However, lopinavir in itself has very low bioavailability. Ritonavir helps to decrease the amount of viral load in the body so your immune system can work better. Ritonavir increases ("boosts") the bioavailability of lopinavir by inhibiting the enzymes responsible for lopinavir metabolism. The drug combination has shown modest activity against SARS-CoV-2 virus.

In a study including 41 patients with SARS, patients that received lopimune showed fewer adverse clinical outcomes of ARDS or death than those that received ribavirin. When used in combination with interferon beta 1-b, the drug demonstrated virologic and clinical improvement in a preclinical study. There is an ongoing randomized controlled trial (RCT) to investigate its effectiveness in combination with interferon beta 1-b in MERS. A recent RCT conducted in China failed to demonstrate any difference in the time to clinical improvement as compared with the usual care. It did not reduce mortality but its use was associated with more adverse events. But, the study was not blinded and had a small number of patients (199) with a small number of the event of deaths. The drug should therefore, not be completely ruled out. The results of the ongoing REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial (NCT02735707) will help better understand the effectiveness of the drug in COVID-19.

Indication
Covid positive mild illness

Contraindication
Pregnancy
Liver disease
Kidney disease

Some of the Side effects
i. Pancreatitis, ii. Renal Impairment, iii. Hepatic Impairment

Dose
200 mg/50 mg 2 tablets Twice daily

3. Favipiravir

It is an oral antiviral drug approved for treatment of mild and moderate COVID-19 patients

Mechanism of Action

The mechanism of its actions is related to the selective and potent inhibition of viral RNA-dependent RNA polymerase, preventing the replication of viral genome. It thus helps in reducing the viral load in the body. This drug was approved in Japan against influenza pandemic. What is of interest is that it has shown antiviral properties against a wide range and subtypes of influenza strains, such as arenaviruses, bunyaviruses and filoviruses, that were resistant to the other anti-influenza drugs. The mechanism of action of favipiravir is novel compared to existing influenza antivirals that primarily prevent entry and exit of the virus from cells.

Published results in COVID-19

Better therapeutic response in terms of disease progression and viral clearance were observed in a study comparing the effects of tablet Favipiravir with Lopinavir-Ritonavir. Shorter viral clearance time, a more significant improvement in chest imaging and fewer adverse events were noted in the group of patients that received Favipiravir plus interferon (IFN)-α as compared to the group of patients that received Lopinavir-Ritonavir plus interferon (IFN)-α. Another RCT comparing Arbidol and Favipiravir in mild to moderate COVID-19 showed that patients receiving Favipiravir had a faster time of fever and cough relief than that in the Arbidol group.

Indication
Covid positive patients, mild or moderate illness.

Contraindication
i. Liver and kidney diseases, ii. pregnant and lactating women, iii. allergic to Favipiravir

Some of the Side effects

i. Diarrhoea,

ii. Increased uric acid levels,

iii. Decreased white blood cells count,

iv. Increased liver enzymes,

v. Psychiatric symptoms

Dose

The dosage is 200 mg X 9 tablets twice on Day 1 and then 200 mg X 4 tablets once a day from Day 2 to Day 7 or 14.

If 400 mg tab give 4.5 tabs twice on Day 1 and then 400 mg X 2 tablets once a day from Day 2 to Day 7 or 14.

4.Remdesivir

Remdesivir possesses broad spectrum antiviral activity against several viruses including Ebola, Nipah, and against the SARS-CoV and MERS.

It is approved for restricted emergency use in moderate to severe COVID-19 patients who are on oxygen support

Mechanism of Action

The drug blocks the action of a viral enzyme named RNA-dependent RNA polymerase and perturbs viral replication causing a decrease in viral RNA production. Remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator.

Remdesivir is a nucleoside analog that is expected to inhibit the action of RNA polymerase.

By incorporating into RNA, additional nucleotides cannot be added, terminating RNA transcription. Remdesivir has shown anti SARS-CoV-2 activity in vitro and in vivo pre-clinical studies.

Viruses with mutations in RNA polymerase to develop partial resistance to remdesivir have been shown to be less infective.

Published results in COVID-19

This drug has shown to shorten hospital stay when used earlier in the illness. In a study including moderate to severe cases of COVID-19 infection, clinical improvement was seen in 36 of the 53 patients following administration. In another study its administration was associated with a shorter hospital stay. A systematic review comparing remdesivir, ribavirin, favipiravir, oseltamivir and umifenovir, showed remdesivir to be the most promising in fighting against COVID-19 .

Indication

It is considered in patients with of moderate to severe COVID-19 (those on oxygen)

Contraindication

i. Patients with known hypersensitivity to any ingredient, ii. deranged LFT, iii. Renal impairment, iv. Pregnancy, lactating females; Children less than 12 yrs

Some of the Side effects

i. respiratory failure, ii. organ impairment, iii. low albumin, low potassium, low count of red blood cells, low count of platelets, iv. raised blood levels of liver enzymes (a sign of liver problems), v. nausea.

Dose

Day 1 loading dose: 200 mg IV infused over 1 hr,

Days 2-5 maintenance dose: 100 mg IV daily (Total 5 days can be extended to 10 days in severe cases).

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21 Corticosteroids

COVID-19 is associated with diffuse lung damage. The widely variable clinical presentation of the disease is mainly associated with an unrestrained hyper inflammatory response to the viral infection seen in the more severely affected cases. This is reflected as an increase in inflammatory markers, including CRP, Ferritin, interleukin-1, and interleukin-6. The ensuing hypercytokinemia, results from the systemic spread of a localized immune response to the viral infection and is responsible for the complications associated with COVID-19 infections, including oxygenation failure and ARDS, formation of micro and macro clots, secondary bacterial infections and multiple organ damage (kidneys, brain, heart), sepsis and even death.

Corticosteroids help reduce inflammation. They help inhibit neutrophil apoptosis and demargination; they inhibit inflammatory transcription factors and promote anti-inflammatory genes like interleukin-10. Corticosteroids may modulate the unrestrained immune response to the SARS-CoV-2 virus infection thereby preventing the development of complications, namely, ARDS, sepsis and even death. Timely and appropriate application of corticosteroids can avoid the need for invasive mechanical ventilation and improve the outcomes of critical patients with COVID-19. Level I evidence has shown that use of systemic corticosteroids in ARDS has shown to reduce mortality and mechanical ventilation. It has also been associated with faster resolution of shock. It is recommended to start corticosteroids within 6 hours of a patient needing oxygen support of ≥ 4 l/min.

Dexamethasone

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressive effects.

An RCT including 2104 patients showed that the group receiving IV or oral dexamethasone had lower mortality rate in the group of patients that were either receiving oxygen or were on invasive mechanical ventilation compared to the group receiving standard care. The difference however was not seen in the group of patients not requiring oxygen/respiratory support.

Indication
Indicated in moderate to severe COVID-19 cases.

Contraindication
i. Allergy to the drug, ii. Severe Hyperglycemia

Some of the side effects

i. Fragile skin, ii. Dry scaly skin, iii. Rashes, iv. Increased appetite, v. Loss of muscle mass, vi.Hyperglycaemia viii secondary bacterial and fungal infections

Dose

Inj. Dexamethasone 0.1 – 0.2 mg/kg for 3-5 Days in moderate COVID-19 cases
Inj. Dexamethasone 0.2 – 0.4 mg /kg for 5-7 Days in severe COVID-19 cases

Methylprednisolone

Methylprednisolone has the benefit of parenteral administration, quicker onset of action and a shorter duration of action compared to dexamethasone. This decreases the risk associated with prolonged use of corticosteroids, including fluid retention, hypokalemia, hypercortisolism and dysglycemia.

A study including 26 patients with severe illness showed that the use of methylprednisolone (1-2 mg/kg/day for 5-7 days) correlated with shorter oxygen use duration and improvement in radiographic signs.

In another case series including 101 patients with severe or critical COVID-19, improved oxygenation was seen with zero mortality following administration of single-dose pulse methylprednisolone (40-500 mg).

Indication

COVID-19 patients with moderate or severe pneumonia (indication of Raised

Inflammatory markers)

Dose

Inj. Methylprednisolone 0.5 -1 mg/kg in moderate cases.
Inj. Methylprednisolone 1-2 mg/kg for 5-7 Days in severe cases.

Contraindication

i. Liver abnormalities, ii. Kidney abnormalities, iii. High uncontrolled diabetes, iv. Pressure Glaucoma, v. insufficiency of the hypothalamus and pituitary gland, vi. high cholesterol, vii. low amount of potassium in the blood, viii. a reduction in the body's resistance to infection

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22 Anticoagulant

Low-Molecular-Weight Heparin (LMWH)

Heparin is an anticoagulant and is classified according to its molecular weight. Enoxaparin is a low molecular weight heparin

Mechanism of action

Deep vein thrombosis (DVT) is known to occur in bed ridden, hospitalized patients. Marone and Rinaldi reported frequent cases of DVT even among non-ICU, hospitalized COVID-19 patients. A significant proportion of patients with severe COVID-19 illness deteriorate due to an underlying hyper inflammatory response to the viral infection leading to a cascade of events and complications including acute respiratory distress syndrome (ARDS), sepsis and septic shock and even death. The hyper inflammatory host response is characterized by the release of several cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF- α). This further activates the vascular endothelial cells, platelets, and leukocytes. Activation of platelets results in release of numerous inflammatory molecules such as inflammatory mediators, growth factors, and proteases. Leukocyte activation results in release of leukotrienes, prostaglandins, bradykinin, and free oxygen radicals. The production of these inflammatory molecules from activation of endothelial cells promotes a procoagulant state and probably enhances leukocyte adhesion to the vein walls causing formation of micro and macro clots. The imbalance between the procoagulation and anticoagulation states promotes fibrin generation. In advanced stages of COVID-19, elevated levels of D-dimer and fibrinogen degradation products have been reported. Fibrin accumulation in the lung is a

hallmark of ARDS. The fibrin clots further limit exchange of oxygen. Multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may improve prognosis.

LMWH is used for anticoagulation prophylactically in covid patients to prevent thromboembolism. If d-dimer levels are high it is used in therapeutic doses to treat coagulopathy in covid patients. It also exhibits anti-inflammatory action probably by binding with inflammatory cytokines, inhibiting neutrophil chemotaxis and leukocyte migration, and protection of the endothelium. In this way heparin may also protect from microcirculatory dysfunction. From earlier experiences with H1N1 patients who developed ARDS, empirical systemic anticoagulation resulted in significant reduction of incidence of venous thromboembolism without increasing hemorrhagic complications. Studies have also demonstrated a potential anti-viral role of heparin through inhibition of viral adhesion to the host cell surface.

Published results in COVID-19

Tang et al. reported lower mortality in severe COVID-19 patients with sepsis-induced coagulopathy (SIC) score ≥4 or D-dimer >6-fold of upper limit of normal.

Thachil et al. found that LMWH in sepsis induced coagulopathy was associated with better prognosis in relation to mortality.

A retrospective controlled study to evaluate the effect of LMWH on disease progression showed that LMWH improved the coagulation dysfunction of COVID-19 patients and exerted anti-inflammatory effects by reducing IL-6 levels. Also, the reduction in levels was significantly different from the control group. Changes in the levels of D-dimer and fibrinogen degradation products in the LMWH group before and after LMWH treatment were significantly different from those in the control group.

Indication

Thromboprophylaxis therapy should be considered in all COVID-19 patients requiring hospital admission unless contraindicated.

If any patient at any time has progressive symptoms, D-dimer to be checked and if high make LMW heparin twice a day in therapeutic dose.

Dose

Prophylactic - Enoxaparin 0.4- 0.6 IU SC once a day

If any patient at any time has progressive symptoms or D-dimer increased,

Therapeutic - Enoxaparin 0.4 - 0.6 IU SC twice a day

In critically ill patients with COVID-19 who have proximal DVT or pulmonary embolism, recommend parenteral anticoagulation therapy with therapeutic weight-adjusted LMWH.

Contraindication

LMWH prophylaxis is to be avoided if

i) There is evidence of active bleeding

ii) Platelet count is less than 25 × 109/L

iii) Fibrinogen level less than 0.5 gm/lit

iv) Recent haemorrhagic stroke

v) Hypersensitivity to enoxaparin, heparin

Drug Interactions

Other anticoagulants, anti-platelets, NSAIDs, salicylates

Adverse effects

Haemorrhage (including at the inj site)- internal or external bleeding e.g hematuria, ecchymosis

Pain at site of injection

Anemia

Thrombocytopenia

Peripheral edema

End stage renal disease (ESRD)

*Note: if LMWH is unavailable or in cases of ESRD use unfractionated heparin (UFH). Need to monitor PT/ INR regularly

Dose of UFH : prophylactic Adult : 5000 units s.c twice daily ; therapeutic : *Adult: 15,000-20,000 U s.c 12 hrly or 8,000-10,000 U s.c 8 hrly. OR 5,000 U (10,000 U in severe pulmonary embolism) IV loading dose followed by 1,000-2,000 U/hr continuous infusion.; Child: 250 U/kg s.c bid. OR 50 U/kg loading dose, followed by an infusion of 15-25 U/kg/hr.*

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Aspirin

Aspirin has multiple effects of inhibiting virus replication, anticoagulation and anti-inflammation. Aspirin has antiviral effect on multiple levels as shown in scientific studies. It can inhibit virus replication by inhibition of prostaglandin E2 (PGE2) in macrophages and upregulation of type I interferon production. It is a well known anti-inflammatory drug and acts by inhibiting cox-oxidase (COX). It also inhibits neutrophil and platelet aggregation.

Indication

1. In asymptomatic / very mild covid positive cases with mild elevation in d-dimer who are in home isolation

2. After discharge from hospital if d-dimer has not yet returned to normal

Dose

Tab Aspirin 75 mg od

Contraindications

Allergic to aspirin

Active bleeding / bleeding disorder

Peptic ulcer disease

Adverse effects

Gastric irritation or bleeding

Thrombocytopenia

Bronchospasm

Allergic reactions

23 IL6 Inhibitors

1.Tocilizumab

Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor.

It was used for treatment of rheumatoid arthritis and systemic juvenile arthritis and is now repurposed for COVID-19

Mechanism of action

Hyper immune responses to the viral infection are responsible for the complications associated with COVID-19 infection, namely, ARDS, sepsis, septic shock and even death. The dysregulated immune system results in production of cytokines such as interleukin-6 (IL-6), which bind to the IL-6 receptors on the target cells, causing the cytokine storm. The hypercytokinemia further leads to pulmonary inflammation and this together with thrombus formation causes alveolar damage and fibrotic healing. As a result oxygen absorption is hindered leading to acute respiratory distress syndrome (ARDS). The dysregulated production of cytokines may also damage other organs including heart, kidneys and brain and predisposes the individual to secondary superadded infections. Anti-cytokine therapy may prevent the cascade of events that follows the host hyper immune response.

Tociluzumab is a humanized monoclonal antibody of the IgG1 class which acts as anti-cytokine agent through inhibition of the interleukin-6 (IL-6) receptor. This blockage of receptors prevents damaging effects of IL-6 and thus prevent disease progression. Tocilizumab, administered intravenously or subcutaneously, has been tested in clinical care for the treatment of severe

COVID-19. Based on the available evidence, the drug's use is accepted off-label by the Indian regulator. It is a very expensive drug and difficult to procure in India.

Published results in COVID-19

In a study conducted in China including 15 patients at risk of cytokine storm, treatment with Tocilizumab demonstrated clinical benefits. A retrospective case-control study showed that Tocilizumab administered in severe cases of COVID-19 may reduce the number of ICU admissions and/or mortality. Another study was conducted in Italy. It included 100 patients with COVID-19 ARDS requiring mechanical ventilation. Following IV infusion of the drug, 69% of patients improved and were successfully off mechanical ventilation. A retrospective observational study showed that intravenous or subcutaneous administration of the drug might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19.

Indication

Markedly Raised IL-6 (usually above 100 pg/ml)

Contraindication

I. liver problems, ii. abnormal liver function tests, iii. tuberculosis , iv. bacterial infection, v. opportunistic fungal infection, vi. pneumonia with a fungus called Pneumocystis jirovecii, vii. Cancer or malignancy, viii. Demyelination

Some of the Side effects

The most common adverse effects of tocilizumab in clinical studies were:

i. respiratory tract infections, ii. Headaches, iii. hypertension, iv. liver injury, v. Injection site reactions (rash, redness, swelling, itching) may also occur, vi. Fungal infections.

Special considerations before its use include

i. Presence of raised inflammatory markers (e.g., CRP>20, Ferritin>300, IL-6>20)

ii. Check procalcitonin level which should be less than 0.5.

iii. Active infections and Tuberculosis should be ruled out before use.

iv. Patients should be carefully monitored post Tocilizumab for secondary infections, fungal infections, persistent fever 101 F, neutropenia and leukocytosis.

v. As Tocilizumab is an IL-6 receptor inhibitor, repeat IL-6 levels within 24 hours are expected to rise.

Dose

8mg/ kg (maximum 400 mg at one time) given slowly in 100 ml NS over 1 hour; dose can be repeated once after 12 to 24 hrs.

2. Itolizumab

The India-based Biocon and the Center for Molecular Immunology (CIM) in Cuba have developed humanized IgG1 monoclonal antibody known as Itolizumab.

It is an anti-CD6 IgG1 monoclonal antibody. It is used to treat moderate to severe chronic plaque psoriasis but now repurposed for COVID-19

Mechanism of action

Itolizumab blocks the domain-1 of CD-6 that is responsible for priming, activation, and differentiation of T-cells. The T-cell proliferation is significantly reduced by Itolizumab along with substantial downregulation of the production of cytokines/chemokines. It is currently being studied for addressing COVID-19 related cytokine storms and its complications.

The action of Itolizumab is immunomodulation of T effector function and its trafficking to the inflammation site, sparing Tregs and preserving the antiviral response, and reducing associated morbidity and mortality. Itolizumab reduces the signature cytokines of hyperinflammation that include IL-2, IFN-γ, TNF-α through Th-1 pathway and IL-17, IL-6, TNF-α through Th-17 pathway.

The action of Itolizumab is upstream at Th-17 and Th-1 and thus downregulates multiple cytokines and chemokines as opposed to Toclizumab which blocks only the specific cytokines released downstream.

Published articles in COVID-19

Itolizumab has been marketed in India since 2013 for the treatment of moderate to severe chronic plaque psoriasis and it was approved by the Drug Controller

General of India (DCGI) in January 2013.

A trial in COVID-19 patients with moderate to severe ARDS in India has been completed by Itolizumab. The study of efficacy and safety of Itolizumab in COVID-19 complications, was a multi-centric, open label, randomized, controlled trial.

The DCGI approval of Itolizumab is based on the results from the successful conclusion of a randomized, controlled clinical trial at multiple hospitals in Mumbai and New Delhi and it is from the DCGI.

The study focuses on the safety and efficacy of Itolizumab in prevention of CRS in moderate to severe ARDS patients due to COVID-19. The primary endpoints were met for the reduction in mortality rate and other key secondary endpoints for efficacy and biomarkers were also achieved.

Indications

- Patients with moderate to severe ARDS, or more than 25% deterioration.
- Baseline serum ferritin level ≥400ng/mL or IL-6 levels, in patients, greater than 4 times the upper limit of normal (ULN)

Dose

- Administration of First IV infusion 1.6 mg/kg in 250 mL of 0.9% normal saline at 50 ml/hr
- Subsequent infusions at 0.8 mg/kg dose weekly could be completed over 3–4 hours (max 4 doses) only if the first infusion is well tolerated.

Adverse reactions

Infusion-related reactions to Itolizumab may include

- Chills
- Rigor
- Nausea
- Flushing
- Urticaria
- Cough
- Hypersensitivity

- Pruritus
- Rash
- Wheezing
- Dyspnea
- Dizziness
- Headache
- Hypertension

Contraindications

- No administration of Itolizumab should be done to patients having a history of severe allergy or known hypersensitivity reaction to any component of Itolizumab or any murine proteins
- Active infections or sepsis
- The studies in paediatric population <18 years old has not been done to study the safety and efficacy of Itolizumab
- Patients having hepatic and renal impairment
- Nursing mothers & pregnancy
- Severe allergic reactions to mAbs
- Active tuberculosis (TB) infection or a history of inadequately treated or latent tuberculosis
- Oral intake of anti-rejection or immune-suppressive drugs in the past 6 months
- A known history of Hepatitis B, Hepatitis C or HIV
- Absolute neutrophils count (ANC) <1000/mm3, platelet count <50,000/mm3 and absolute lymphocyte count (ALC) <500/mm3

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24 Antibiotics

1.Azithromycin

Mechanism of Action

Azithromycin (AZM) is a promising drug candidate for the treatment of the COVID-19. It is a broad spectrum antibiotic which has both gram + and gram - coverage. Azithromycin may be used in combination with other antibiotics when it's used to treat infections. Anti-inflammatory effects of azithromycin include modulating the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-1β and acceleration of phagocytosis by macrophages. This classifies azithromycin as a senolytic drug that selectively attacks and kills senescent cells with an efficiency of almost 97%. AZM has shown antiviral effect in vitro against Zika and Ebola viruses. It is also known to prevent severe respiratory tract infection in patients suffering from viral infections. It inhibits protein synthesis and reduces viral replication. Combination of AZM with Hydroxychloroquine (HCQ) have been said to act synergistically and enhance the antiviral and anti-inflammatory effects of the drugs. A controlled trial including 20 mild hospitalised COVID-19 patients showed that those treated with HCQ+AZM showed a significant reduction of viral carriage and a more effective viral clearance compared with treatment with those treated with HCQ alone suggesting a synergistic effect of the combination of hydroxychloroquine and azithromycin. However, this drug combination is associated with prolongation of QTc and ECG monitoring is recommended when using this drug combination.

Indication

COVID contacts with sore throat or cough
COVID suspects with mild respiratory symptoms - with HCQ (check ECG and age <60 yrs)
Mild COVID positive patients who do not have cardiac/ ECG abnormalities and age <60 yrs -with HCQ

Contraindication

Allergy to macrolides
QT interval prolongation
abnormal heart rhythm
Hypersensitivity to drug

Side effects

Diarrhea or loose stools,
Nausea,
Abdominal pain,
Stomach upset,
Vomiting,
Constipation,
Dizziness,
Tiredness,
Headache,
QT interval prolongation , cardiac arrhythmia
Anaphylaxis
Nervousness,
Sleep problems (insomnia),
Skin rash or itching,
Ringing in the ears,
Hearing problems,
Decreased sense of taste or smell.

Dose

Typical dosage is 500 mg po once per day for 3 - 5 days

2. Doxycycline

Mechanism of Action

Doxycycline is a broad-spectrum tetracycline antimicrobial agent; it exhibits anti-inflammatory effects along with in vitro antiviral activity against several RNA viruses.

Doxycycline emerges as an antimicrobial agent possessing antiviral and anti-inflammatory activities; which by dampening the critical cytokine storm has the potential to prevent lung damage.

In COVID-19, elevated levels of blood interleukin (IL)-6 have been more commonly observed in severe COVID-19 illness suggesting that mortality might be due to virally-driven hyperinflammation and to cytokine storms. Importantly, doxycycline reduces the pro- inflammatory cytokines, including IL-6.

Published results in COVID-19

Patients in long term care facilities are at a high risk of contracting COVID-19 due to age and comorbidities. A case series including suspected or confirmed COVID-19 patients from such a health care centre, showed that early administration of Doxycycline-Hydroxychloroquine combination therapy resulted in clinical recovery, decreased transfer to hospital and decreased mortality.

An RCT to compare effectiveness of Hydroxychloroquine and Azithromycin with Ivermectin and Doxycycline in mild to moderate COVID-19 patients was conducted. The study showed a faster recovery in the group that received Ivermectin and Doxycycline with fewer adverse effects and better patient compliance compared to those in the Hydroxychloroquine and Azithromycin Group.

Indication

Can be used with Ivermectin if Tab HCQ/Tab Favipiravir is contraindicated,
Cap Doxycycline 100mg 1-0-1 for 5 days + Tab Ivermectin 12mg 1-0-0 for 3 days
COVID contacts
COVID suspects
Mild COVID positive patients

Contraindication

i. Hypersensitivity to drug, ii. Pregnancy, iii. Children less than 8 yrs.

Side effects

I. Diarrhea, ii. Difficulty swallowing, iii. Drug rash, iv. Esophageal ulcer, v. Esophagitis, vi.

Facial redness, vii. Headache, viii. Loss of appetite, ix. Microbial overgrowth including fungi,

x. discolouration of teeth, xi. Photosensitivity, xii. increased serum AST, xiii. Arthralgia, xiv. myalgia.

Dose

100mg twice a day it can be given Orally / IV

3. Ivermectin

Ivermectin is anti-paras drug which is repurposed for COVID-19

Mechanism of Action

It is an inhibitor of COVID-19 causative virus (SARS-CoV-2) in vitro. The viral replication is inhibited by Ivermectin.

Ivermectin has efficacy of reduction in virus by ~5000-fold at 48 hour in cell culture in a single treatment.

Ivermectin is a well-known anti-helmintic agent from the late-1970s. It causes stimulation of gamma amino butyric acid (GABA)-gated-Cl− channels which leads to hyperpolarization, and resulting in paralysis of the infesting organism.

An antiviral activity against broad range of many other viruses has been shown in previous studies. It is effective as an antiviral treatment for SARS- CoV-2 if given to patients early in infection. Ivermectin helps in limiting the viral load along with person-person transmission and to prevent severe disease progression.

Ivermectin is a macrocyclic lactone with a broad-spectrum antiparasitic pharmacological activity Of the entire class of avermectins, Ivermectin is the safest and most effective semi-synthetic derivative.

It acts as an inhibitor of nuclear transport mediated by the importin $\alpha/\beta 1$ heterodimer, responsible for the translocation of various viral species proteins

(HIV-1, Sv40), indispensable for their replication. A considerable number of RNA viruses is affected by this inhibition.

Ivermectin has an established safety profile. The activity against SARS-CoV-2 is the discovery of Ivermectin which has given reason for hope.

Indications

Can be used with Doxycycline if Tab HCQ/Tab Favipiravir is contraindicated, for following category

- Covid contacts
- Covid suspects
- Mild Covid positive patients

Adverse Reactions

- Mazzotti reaction (e.g. oedema, pruritus, urticaria rash, lymphadenitis, arthralgia, synovitis, fever, sore throat, cough, headache, tachycardia, orthostatic hypotension).
- Dizziness
- Fatigue
- Drowsiness
- Vertigo
- Tremor
- Diarrhoea, abdominal pain, constipation, nausea, loss of appetite , vomiting.
- Hepatic: Increased serum ALT, AST.
- Decreased WBC
- Skin redness, burning sensation, irritation, itchiness, dry skin, contact dermatitis

Dose

- Tab Ivermectin 12 mg po od for 3 days

Dose for Prophylaxis:

Tab. Ivermectin 12 mg On Day 1, Day 7 and Day 30 (2 hrs after dinner) Followed by 1 Tab of 12 mg every 30 days till pandemic is over This is to be taken by all high risk people and frontline health workers. It reduces severity of disease and fatality in 80-90%.

4. Cephalosporins

Antibiotics are used to treat superimposed bacterial infections in Covid patients.
For treatment of moderate to severe pneumonia in Covid patients, 2 nd or 3 rd generation cephalosporin antibiotics are being used.
Second-generation cephalosporins are more active against gram-negative bacteria, with less activity against gram-positive bacteria than 1 st generation . e.g Cefuroxime, Cefoxitin Third generation are most active against gram-negative bacteria, with less activity against gram-positive bacteria than 1st & 2nd generation. E.g. Ceftriaxone, Cefoperazone, Cefixime,
Cefotaxime etc
Cefoperazone +Sulbactum is used to treat pseudomonas bacterial infections
Always watch for any previous history of allergies
To describe all cephalosporins, is beyond the scope of this book

Some Common Doses are

Cefuroxime :

Adult : IV 1.5 g bid, followed by an oral dose of 500 mg bid for total 7 -10 days

Child: ≤3 wk 30-100 mg/kg daily by IV inj given as 2 or 3 divided doses; >3 wk <40 kg: 30-100 mg/kg daily by IV inj given as 3 or 4 divided doses; 60 mg/kg daily to most infections.

Ceftriaxone

Adult: IV 1-2 g daily, given once or in 2 divided doses infused over at least 30 minutes,

Child: <15 days 20-50 mg/kg once daily via IV infusion over 60 minutes; 15 days to 12 years weighing <50 kg: 50-80 mg/kg daily, may be increased to 100 mg/kg for severe infections via IV infusion over at least 30 minutes. Max: 4 g daily; >12 years weighing ≥50 kg: Same as adult dose.

Cefoperazone (1000mg) + Sulbactam (500mg)

Adult : IV 1.5 g bid for 7 to 10 days

5. Meropenem

Mechanism of Action

Meropenem is a broad spectrum beta-lactam antibiotic, effective for both gram negative and gram positive bacteria, including pseudomonas.Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to

reach targets and interfere with the synthesis of the vital cell wall components, which leads to cell death.

Indication

Moderate to Severe Pneumonia in Covid positive patients
Long standing infections which are not reacting to lower antibiotics
Pneumonia
Lower respiratory tract infection
Contraindication -
Allergic to carbepenem
Anaphylactic reaction to beta-lactam (penicillin , cephalosporins)
Caution in following
Pregnancy
Lactation
Thrombocytopenia
Chronic Kidney disease
Blood disorders
Lesion in brain
Seizure

Side effects

Injection site discomfort
Nausea
Vomiting
Diarrhoea
Abdominal discomfort
Confusional states and seizure
Rash
Raised liver enzymes

Dose

Adult : IV 0.5-1 g tds via infusion over approx 15-30 minutes

Child: ≥3 months weighing ≤50 kg: 10-20 mg/kg tds IV via infusion over approx 15-30 minutes >50 kg: Same dose as adult.

6.Piperacillin-Tazobactam

Mechanism of Action

Piperacillin acts by inhibition of cell wall synthesis and bacterial septum formation in susceptible bacteria. The bactericidal activity is initiated via inhibition of bacterial cell wall synthesis by binding one or more of the penicillin binding proteins (PBPs).

Tazobactam is a penicillanic acid sulfone derivative. It has β-lactamase inhibitory properties.

Tazobactam enhances the activity of piperacillin against β-lactamase-producing bacteria.

Piperacillin and Tazobactam has a wide range of activity against gm+ve and gm-ve aerobic and anaerobic bacteria.

In COVID-19 patients Piperacillin-Tazobactam is used in ICU cases which are associated with pneumonia.

Indication

Moderate to Severe Pneumonia in Covid positive patients
Pneumococcal infection
Nosocomial Pneumonia
Higher chest Infections
Nosocomial pneumonia caused by P aeruginosa should be treated in combination with an aminoglycoside.

Contraindication

Hypersensitivity to any penicillin
History of acute severe allergic reaction to any other β-lactam active substances (e.g. cephalosporin, monobactam or carbapenem)
Allergic to Tazobactam

Side effects

Diarrhoea
Headache
trouble sleeping
Rash
Nausea
Constipation
Thrombophlebitis
Thrombocytopenia
Anaphylaxis
Antibiotic-induced pseudomembranous colitis

Dose

Adult - 4.5 gm IV 6hrly by infusion over 30 min for 5-14 days. (piperacillin 4 g and tazobactam 0.5 g) If used empirically, combine with aminoglycoside or antipseudomonal fluoroquinolone

Child: 2-12 yr 90 mg/kg (piperacillin 80 mg/kg and tazobactam 10 mg/kg) 6 hrly for 5-14 days by infusion over 30 min. Max: 4.5 g per dose, >12 yr Same dose as adult Dose adjustment required for renal impairment

7. Teicoplanin

Teicoplanin is an antibiotic used in treatment of serious infections caused by Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus, Clostridium and Enterococcus faecalis. Drug levels need to be monitored Details are beyond scope of this book

8. Sepsivac

Sepsivac is an immunotherapy treatment and is introduced by Cadila Pharmaceuticals. In sepsis management, it is first-in-the-world innovation. The Drug Controller General of India (DCGI) has approved the drug for immunotherapy treatment in sepsis or septic shock.

It is Mycobacterium w (Heat Killed) Injection.

Mechanism of Action

Sepsivac is an immunomodulator which is a non-pathogenic mycobacterium.

Sepsivac effectively saves more lives in sepsis consequent of the immunomodulatory effect. The regulation of the host immune response is helped by Sepsivac drug.

A lot of pro-inflammatory and anti-inflammatory cytokines are generated in the body in response to an infection to stimulate the production of antibodies in patients with sepsis. The inflammation in the organs of the body is caused by some of the cytokines which might be harmful. The efficacy of Sepsivac is to reduce the mortality in critically ill COVID-19 patients.

Sepsivac, an immunomodulator drug, regulates this host immune response. Sepsivac has no systemic side effects and is found to be safe in patients. Sepsivac can be used in combination with other treatments to manage a patient in a critical care setting.

Immunomodulators or biological response modifiers have been popular since long. The biological response of individuals to various pathological conditions/disease are altered by them.

The one such agent is Mycobacterium w cells. It contains an active drug substance, a heat killed Mycobacterium w. When administered intradermally, a potent cell mediated immune response is elicited. The cytokines liberated by excited T cells determine cell mediated immune responses that are designated as the Th1 type or Th2 type. The cytokines such as Interferon Gamma, Interleukin - 2 are in association with Th1 response. There is a harmony between Th1 response and Th2 response in normal healthy individuals. The decrease in Th1 response is in association with certain diseases. These include leprosy and malignancy and such conditions improves Th1 response which is associated with improved outcomes.

The chances of high infection and septicemia are present in critically ill COVID-19 patients.

The immune system of the body is modulated by Sepsivac. Therefore, the cytokine storm is inhibited that leads to reduction in mortality and faster recovery.

Published article in sepsis

In a study, 72 patients having gram negative severe sepsis/septic shock were enrolled in phase IIa with escalating dose levels of Mycobacterium w (Heat

Killed) injection over initial 3 days with standard therapy versus standard therapy alone. Clinical and microbiological resolution, was seen significantly in both 0.2 and 0.3 groups.The patients receiving 0.3 Mycobacterium w (Heat Killed) injection had the earliest efficacy with 83% of the patients recovering on day 15 and 100% on day 22 as compared to other groups receiving lesser doses as well as the standard treatment group. There was significant early recovery of organ function including renal and respiratory, multisystem organ failure, fever, and an early improvement of SOFA score. 2 patients in the 0.3 group had mild local reactions. The significant elevation at baseline of cytokine levels in all groups had a more significant fall in 0.3 group compared to other treatment groups. The study showed the efficacy of 0.3 Mycobacterium w (Heat Killed) injection dose in early organ function recovery and microbiological resolution. It serves as a promising novel immunomodulatory therapy in improving outcome in severe Gram Negative Septic Shock.

Another randomized double blind study showed significant reduction in the days on mechanical ventilation, ICU and length of hospital stay along with lower incidence of ventilator associated pneumonia and secondary bacterial infections by the use of Mycobacterium w (Heat Killed) in severe sepsis .

In review of another study, the objective to reduce the 28 days mortality associated with sepsis was met using Mycobacterium w (Heat Killed) as an adjuvant to standard treatment in sepsis.

This study also showed significant reduction in days on mechanical ventilation, ICU and hospital length of stay, lower incidence of multi-organ failure (SOFA score).

Indications:

- Critical care covid patients
- Covid positive with severe infection
- As an adjuvant to the standard treatment in covid patients with sepsis (due to gram Negative infections)

Contraindications:

- Allergy or Hypersensitivity to the drug.
- Mycobacterium w (Heat Killed) injection is contraindicated in:

  a) An allergic reactions history to Mycobacterium w (Heat Killed) injection or

any of the excipients

b) Fever

c) In pregnancy and lactating women

- In patients with generalized septic skin conditions (if eczema exists, a site should be chosen that is free from skin lesions).

- In chronic debilitating condition other than the proposed indication

Side effects:

- Diarrhoea
- Rashes/ erythema
- Headache
- Ulceration and abscesses
- Keloid formation at the injection site
- Anaemia, Leukopenia, Neutropenia as treatment-emergent hematologic toxicities
- Increased transaminase and alkaline phosphatase levels
- Nausea and vomiting
- Pain, weakness
- Weight loss
- Anorexia
- Neuropathy
- Constipation
- Breathlessness
- Loss of appetite
- Cough
- Haemoptysis
- Reactogenic reactions
- Neuropathy and alopecia
- In patients with sepsis- transfusion associated reaction, thrombocytopenia, Hypokalemia, Transaminitis, Local site reaction, Hyponatremia, Hypokalemia, Respiratory system involvement, Deranged RFT.

Dose:

- Intradermal injection 0.3ml of Mycobacterium w (Heat Killed) injection is given in three divided doses of 0.1 ml each on three different sites daily for

three days.

- Mycobacterium w total dosage is 0.9 ml over a period of three days.

Drug Interactions:

- There is no known to have any drug-drug interactions to Mycobacterium w (Heat Killed) injection.
- The body's own immune response even when administered with other drugs like

cytotoxic, anti-leprosy drugs is induced by Mycobacterium w (Heat Killed) injection.

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25 Vitamins and Minerals

1.Vitamin C

Vitamin C is a major water-soluble vitamin. It is an antioxidant acting as a free radical scavenger.

Mechanism of Action in COVID-19

It is an important vitamin exerting antiviral properties through cytokine modulation, reduction of inflammation, supporting lymphocyte activity and restoring mitochondrial function.

There is a considerable body of evidence suggesting its effect on the immune system. During infection, vitamin C accumulates in polymorphonuclear leukocytes and enhances chemotaxis and phagocytosis. It promotes apoptosis and used neutrophil clearance from sites of infection, thus reducing the risk of tissue damage.

It also boosts immunity and enhances the body's defence mechanism. It may play a role in antibody production by supporting differentiation and proliferation of B- and T- cells.

It is also known to enhance endothelial synthesis and type IV collagen for blood vessel basement membrane formation. Its deficiency has been seen to be associated with vascular dysregulation and sepsis. Also, Vitamin C levels have been found to be low in patients with viral infections, ARDS and Sepsis. Conversely, supplementation with Vitamin C has shown beneficial effects in viral infections.

Previous studies have shown that Vitamin C administration inhibited replication of some viruses such as herpes simplex virus, poliovirus, and influenza. In a clinical study involving USSR soldiers with severe viral infection, Vitamin C supplementation was found to be associated with protection against influenza related pneumonia and shorter hospital stay.

Individual case reports of virus induced ARDS have demonstrated clinical benefit through administration of IV Vitamin C.

Published studies in COVID-19

Favourable results of decrease in supplemental oxygen requirement and inflammatory markers following administration of IV vitamin C in moderate to severe cases of COVID-19 were seen in a case series including 17 patients. A double blind, randomised controlled study with 167 critical COVID-19 patients with ARDS and sepsis did not show difference between those receiving IV Vitamin C and those receiving placebo. In this study, a 96 hour infusion of Vitamin C did not significantly decrease inflammatory marker levels or improve organ dysfunction scores.

Another trial to study its effects on severe COVID-19 is underway. Also, a Phase 2 trial to test whether hydroxychloroquine, Vitamin C, Vitamin D, and Zinc can prevent COVID-19 symptoms is ongoing.

Indication

- Prophylactic - In healthy individuals , COVID contacts, and COVID suspects
- Therapeutic-all confirmed cases of COVID-19 (asymptomatic, mild, moderate and severe)

Contraindication

- G6PD Deficiency
- Active bleeding
- Hemochromatosis
- History of renal oxalate stones, renal impairment or renal failure

Side effects

- In especially predisposed patients, it may induce gouty arthritis and uric acid stone formation.

- It may induce nervous system disorders including headache, and insomnia.
- May induce gastrointestinal disorders including diarrhea, nausea, vomiting, abdominal and gastrointestinal pain.
- Renal and urinary disorders associated with the production of oxalate, urate or cystine stones.

Dose

- Prophylactic - 500 mg to 1 g orally BD
- Therapeutic

  i. Asymptomatic/ Mild cases - 1 g orally BD
  ii. Moderate cases - 1gm IV tds or 1.5g BD
  iii. Severe cases - 3g IV BD or TDS

Drug Interactions

- May interfere with response to oral anticoagulants.
- Ascorbic acid can promote iron absorption, especially in people with iron deficiency
- Concurrent use of deferoxamine with high doses of ascorbic acid may potentiate iron tissue toxicity resulting in impaired cardiac function and cardiac decompensation.
- Ascorbic acid should not be administered during the first month of deferoxamine treatment.

2.Vitamin D

Vitamin D is a steroid produced in the skin from 7-dehydrocholesterol following ultraviolet B exposure.

Mechanisms of action :

It possesses protective effects against bacterial and viral acute respiratory tract infection. It strengthens the physical epithelial barrier. Viruses disturb the barriers and allow for increase in infection by the virus and other microorganisms. It induces antimicrobial peptide cathelicidin which exhibits direct antimicrobial action against enveloped and nonenveloped viruses. Vitamin D also enhances cellular immunity.

Administering Vitamin D reduces the expression of pro-inflammatory cytokines such as TNFα and IFNγ and increases the expression of anti-inflammatory cytokines. Vitamin D supplementation has also been shown to enhance the expression of genes such as glutathione reductase that are related to antioxidation. In view of the underlying pathology of progression of COVID-19 to ARDS and sepsis, and the beneficial effects of Vitamin D, its administration may be beneficial for minimizing alveolar damage.

Level I evidence has shown Vitamin D to have a 12% overall protection against bacterial and viral acute respiratory infections. Further, when Vitamin D deficiency was corrected with supplementation, there was a 70 % overall protection against respiratory infections. Several observational studies and clinical trials have demonstrated that Vitamin D supplementation lowered the risk of influenza. Serum Vitamin D levels tend to reduce with age. Use of some drugs such as antiepileptics, antineoplastics, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine drugs, and some herbal medicines reduce 25(OH) D concentrations in the body. In view of the benefits of Vitamin D supplementation and the risk of mortality associated with deficiency, Vitamin D supplementation is recommended. Thus, people who are at a higher risk of vitamin D deficiency during the COVID-19 pandemic should be advised Vitamin D supplements to maintain the circulating 25(OH)D in the optimal levels (75–125 nmol/L).

Dose:

In COVID-19 patients (Asymptomatic, mild, moderate and severe cases):
Inj Vit D3 3-6 lac unit IM stat dose.
Or Oral Vit D3 60 k units for 3 days
Maintenance dose Oral Vit D3 60 k units once a week for 6 weeks and then once a month
Optimum Target vit d3 levels 50 - 80 mcg/dl

Side effects:

Usually no side effects seen

Rarely : Chest pain, shortness of breath, Weakness, Weight loss, Constipation, nausea and vomiting

Drug interactions:

- Seizure drugs, Phenobarbital and Dilantin affect Vitamin D metabolism

- Antituberculosis drugs affect Vitamin D metabolism
- Statins increase Vitamin D levels.

3.Vitamin E

Vitamin E is a fat soluble compound and a lipid component of biological membranes.

It consists of eight isoforms, four tocopherols and alpha, beta, gamma & delta tocopherols), and four tocotrienols (and alpha, beta, gamma & delta tocotrienols). The human vitamin E requirements are met by only Alpha tocopherol. The alpha tocopherol is predominantly found in human diet sources such as nuts like almonds and hazelnuts; legumes, such as peanuts; as well as avocados and sunflower seeds.

Mechanism of Action in COVID-19

The absorption of Vitamin E is via the small intestine and it is metabolized, regulated & excreted by the liver.

Vitamin E is a potent antioxidant. It neutralizes the free radicals and donates a free hydrogen ion from its chromanol ring.

The peri oxidative decomposition is caused by the reaction of free radicals (generated from metabolic processes) with polyunsaturated fats within the cell membrane.

The greater levels of lipid peroxidation resulted in Vitamin E deficiency. It has shown clinically by an inverse relationship between vitamin E in ARDS patients and plasma lipoperoxidase.

Vitamin E enhance an immune response through following mechanisms: (Fig 1)

1.Decreased production of nitrogen oxide resulting in prostaglandin E2 down regulation and inhibition of cyclo-oxygenase-2

2.Initiation of T lymphocyte signals

3.Modulation of Th1/Th2 balance

The cell membrane integrity and improvement in the adaptive immune system response to viral respiratory tract infections are the antioxidant properties of Vitamin E derivatives.

An immunomodulatory effect of vitamin E is undertaken through protein kinase C (PKC). The inhibition of PKC affects the proliferation of monocytes, macrophages, neutrophils, and smooth muscle cells and reduces superoxide free radical production in neutrophils and macrophages.

Vitamin E enhances T lymphocyte-mediated immune function with response to mitogens and IL-2 but also neutrophil and natural killer function.

The one of the driving pathological mechanisms is an oxidative stress that supports the biology of ARDS as a result of COVID-19. The excessive lipid peroxidation and failure of biological membranes are resulted by the oxidant-antioxidant balance shift. The pathological outcomes such as the diffuse alveolar damage, hyaline membrane formation, and pulmonary edema are seen in the most severely affected. The production of superoxides is lowered with ingestion of Vitamin E. It also tilts the balance back in favor of antioxidants.

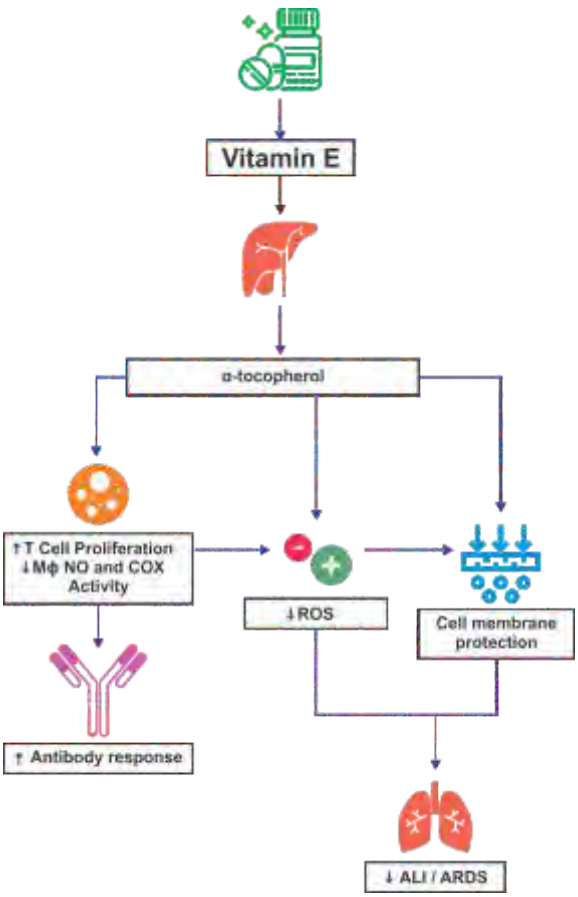

Fig 1 - Vitamin E and anti- COVID-19 mechanism of action in ARDS

Published studies in COVID-19

The benefits of vitamin E supplementation and upper respiratory tract infections have been shown in clinical trials. A reduction in incidence of upper respiratory tract infections has shown with randomization of 617 nursing home residents receiving 200 IU per day for a year of vitamin E. The acute onset protein rich pulmonary edema are the characteristics of ARDS. The exudative phase is referred to as an initial phase of the pathological mechanism. The upregulation of granulocytes, releasing reactive oxygen species (ROS) is resulted by complement activation. This ROS results in the lipid peroxidation in cell membrane, which further resulted in increased permeability and loss of integrity. It has been illustrated in lung parenchyma that results in increased protein permeability. An indicator of plasma lipid peroxidation that is high High thiobarbituric acid reactive substances (TBARS) and low alpha-tocopherol levels have been recognized previously in critically ill patients.

To control the dependency of plasma tocopherol concentrations on the level of circulating lipids, one study specifically examined the tocopherol level as related to plasma total lipid (tocopherol:lipid ratio). It showed a specific deficiency in ARDS patients as compared to non-ARDS patients. During ARDS, a combination of excessive ROS formation and lipoperoxidation and septicemia result in a consumptive loss of vitamin E due to its antioxidant effect.

Indication

- Prophylactic: In healthy individuals, Covid contacts and Covid suspects
- Therapeutic: In all confirmed cases of COVID-19 (asymptomatic, mild, moderate & severe)

Contraindication

- High dosage of vitamin in patients on anticoagulant medicines

Side effects

- High risk of bleeding
- Allergic reactions: hives, swelling of face, throat, tongue & lips.

Dose

- 400 IU once or twice daily

Drug Interactions

- High dosage of vitamin E supplements may interfere & alter the activities of the drugs such as aspirin, warfarin, tamoxifen and cyclosporine aspirin, warfarin, tamoxifen and cyclosporine A

- High dosage of vitamin E can exacerbate the blood coagulation defect of vitamin K deficiency caused by malabsorption or anticoagulant therapy.

4.Vitamin B

Vitamin B are water soluble vitamins (B1, B2, B3, B5, B6, B7, B9, and B12). It plays an important role in cell metabolism.

Mechanism of Action in COVID-19

Vitamin B complex might regulate cytokine/chemokine generation and mediate interaction with immune cells concerned in pathophysiological pathways and inflammation.

In both innate and adaptive immune responses, vitamins B6, B12, and folate play important and complementary roles. It has granted health claims in the European Union for contributing to the normal function of the immune system.

Pyridoxine plays a key role in the production of T cells and interleukins along with lymphocyte maturation.

The conversion of pyruvate to acetyl-CoA is inadequate when thiamine levels are insufficient. This results in impaired aerobic respiration and a compulsory shift to the anaerobic pathway which further results in elevated serum lactate.

For the generation of NADPH and glutathione cycling which is an important antioxidant pathway, thiamine and niacin is needed. The basis of thiamine administration in critically ill populations are formed by these pathways which show reduced lactate and improved mortality in a trial of patients with septic shock. The benefit of thiamine (200 mg every 12 h) in combination with vitamin C (1500 mg every 6 h) and hydrocortisone (50 mg every 6 h) in people with sepsis have shown a particular relevance in a number of studies. It leads to dramatic improvements in organ injury, time to shock reversal, and mortality as well as severe pneumonia.

The action of Vitamin B12 is to be an immunomodulatory factor and to enhance the number of cytotoxic T cells against viral infections. It might also be used as a therapeutic agent in sepsis and systemic inflammatory response syndrome

(SIRS). The normal function of macrophages is maintained by vitamin B12. It has an anti-inflammatory effects in regulation of nuclear factor-κB (NF-κB), a key activator of the pro-inflammatory pathways. Vitamin B12 also has a role in bacteriostasis and phagocytosis.

It might be a possible inhibitor of the RNA-dependent-RNA polymerase activity of the SCV2-nsp12 enzyme. The inhibition of this enzyme can result in lower viral titers and reduce the severity of the COVID-19 disease as this enzyme is critical for the replication of the viral enzyme.

Indication

- Prophylactic: In healthy individuals, Covid contacts and Covid suspects
- Therapeutic: In all confirmed cases of COVID-19 (asymptomatic, mild, moderate &severe)

Thiamine (B1)

Dose:
Adult:

- 10-25 mg/day in single or divided doses in oral treatment .
- ≤300 mg/day IV/IM in thiamine deficiency
- Wernicke-Korsakoff syndrome: Initial- 100 mg by slow IV, then 50-100 mg/day IM/IV till patient can take oral thiamine.

Adverse Reactions
In case of IV administration
- Warm sensation
- Tingling
- Pruritus
- Pain
- Urticaria
- Weakness
- Sweating
- Nausea
- Restlessness
- Tightness of the throat
- Angioedema

- Respiratory distress
- Cyanosis
- Pulmonary oedema,
- GI bleeding,
- Transient vasodilation
- Hypotension,
- Vascular collapse
- Fatal anaphylactic shock in very rare cases

Pyridoxine (B6)

Dose:
Adult:

- Up to 150 mg/day in oral treatment and prevention of vit B6 deficiency

Drug Interactions

- Greater requirement in pyridoxine dose may be required in isoniazid, penicillamine and oral contraceptives
- The effects of levodopa, phenobarbitone, altretamine and phenytoin is reduced

Adverse Reactions

- With long-term administration of large doses may result in severe peripheral neuropathies .

Methylcobalamin (B12)
Dose:
***Adult**:*

- 500 mcg TID oral intake in vitamin B12 deficiency
- 500 mcg IV/IM 3 times weekly for 2 months
- For maintenance 500 mcg OD

Adverse Reactions

- Gastrointestinal disorders: Nausea, vomiting, diarrhoea, abdominal pain.
- General disorders and administration site conditions: Hot sensation, diaphoresis, pain/induration (IM).
- Immune system disorder: Rarely, hypersensitivity reaction e.g. rash, dyspnoea

5.Zinc

It is an essential trace mineral required for multiple vital functions of body.

Mechanism of action:

For normal development and function of cells mediating nonspecific immunity such as neutrophils and NK cells, zinc is a crucial element. To have an effective immune function, a good zinc status is recommended.

The replication of SARS coronavirus (SARS-CoV) and other RNA viruses was inhibited by high concentration of intracellular zinc and it is through inhibition of RNA polymerase.

The improvement in ciliary clearance not only improves the removal of virus particle but also reduces the risk of secondary bacterial infections.

Zinc plays an essential role in preserving tissue barriers.

Zinc supplementation prevents the viral entry and also suppresses its replication,and it also supports the anti-viral response of the host cells. Zinc increases the ciliary length and movements and also sustains tissue integrity. Hence, entrance of the virus is impeded.

The overshooting immune reactions and the ratios of the various immune cell types is normalized by zinc. The high levels of inflammatory mediators including reactive oxygen are prevented by zinc.

The fusion with the host membrane is prevented by zinc. It decreases the viral polymerase function, impairs protein translation and processing, blocks viral particle release, and destabilizes the viral envelope. Zinc has a role as second messenger and importance in regulating intracellular signaling needs of zinc for lymphocyte development and function.

The lymphopenia can be reversed by zinc supplementation.

Zinc could decrease thrombus formation in a clinical context was indicated and a functional association between zinc and ROS production in platelets was described.

After mechanical and inflammation-mediated damage, balanced zinc homeostasis is essential

for wound healing and tissue recovery. This adds more potential benefits of zinc supplementation of COVID-19 patients.

The lung injury is ameliorated by zinc supplementation, thus by reducing neutrophil recruitment and activity

Indications

- Prophylactic: In healthy individuals, Covid contacts and Covid suspects
- Therapeutic: In all confirmed cases of COVID-19 (asymptomatic, mild, moderate &severe)

Contraindications:

- Iron and copper deficiency

Dosage:

Tab Zinc 50mg once a day

- The prescription of zinc as an adjuvant therapy is in different forms of Zn salt, such as Zn-gluconate, Zn-acetate, Zn-sulfate, and Zn-picolinate. In each salt, the amount of elemental Zn is varied.
- 23% elemental Zn is contained in Zn-sulfate. Therefore, for consumption, a 50 mg of
- Zn and a 220 mg of Zn- sulfate tablet would be required.
- The recommended daily allowance of Zn will vary according to the age, sex, and health conditions of an individual.

Drug interaction:

- The absorption of tetracycline is diminished by the concurrent administration of zinc salts. the inhibition of iron and copper absorption occurs in large doses
- Zinc excretion is reduced in amiloride that leads to its accumulation in the body.
- The absorption of zinc is inhibited by the consumption of fiber-containing foods, then take the medicine an hour before, or two hours after, consumption of food high in fiber.

Adverse effects:

- Abdominal pain,
- Dyspepsia and
- Diarrhea
- Fertility, pregnancy and lactation is not affected
- Accumulation of zinc in the body leads to toxic side effects, such as metallic taste sensation, vomiting, and stomach problems

Zinc supplementation

- Improves the mucociliary clearance
- Strengthens the integrity of the epithelium
- Decreases viral replication
- Reserves antiviral immunity
- Attenuates the risk of hyper-inflammation
- Supports anti-oxidative effects
- Reduces lung damage
- Minimizes secondary infections

Published studies in COVID-19:

The reduction in symptom severity, frequency, and duration of the common cold after zinc administration has been shown in studies.

Studies showed reduced symptom severity, reduced frequency, and duration of the common cold after zinc administration.

6. Magnesium

It is an essential mineral required for more than 300 enzymatic reactions of the body.

Mechanism of action

Since magnesium levels are rarely monitored in the clinical setting, hypomagnesemia is a relatively common clinical occurrence that often goes unrecognized. The second most abundant intracellular cation after potassium is magnesium. It has involvement in many enzymatic reactions in the body along with those contributing to the exaggerated immune and inflammatory responses exhibited by COVID-19 patients.

The several aspects of magnesium nutrition warrant clinical consideration is supported by the peer-reviewed literature. The "calcium-channel blocking" effects are included in mechanisms that lead to downstream suppression of nuclear factor-Kβ, interleukin-6, c-reactive protein, and other related endocrine disruptors. It has its role in regulating renal potassium loss; and its ability to activate and enhance the functionality of vitamin D.

CRP levels in individuals with inflammation (CRP levels > 3 mg/dL) are reduced by magnesium supplementation.

Magnesium has an importance in maintaining endothelial function and, therefore, vascular integrity. The deficiency of magnesium induces a pro-inflammatory phenotype, which means increased release of chemokines and cytokines as well as increased thrombogenicity. The platelet-dependent thrombosis is predicted by magnesium. The proper lung function is maintained & reduced risk of airway hyper-reactivity and wheezing is a role of magnesium.

A significant reduction in proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support was incorporated with Vit D, Magnesium, Vit B12 combination in older COVID-19 patients.

Indication

- Prophylactic: In healthy individuals, Covid contacts and Covid suspects
- Therapeutic: In all confirmed cases of COVID-19 (asymptomatic, mild, moderate & severe)

Dose
Tab Magnesium 500 mg po daily

Contraindications:
- Parenteral: Heart block, severe renal impairment, myocardial damage.

Special Precautions:

- Renal impairment
- Myasthenia gravis
- Digitalised patients
- Pregnancy
- Monitor serum-magnesium concentrations.

Drug Interactions:

- In oral administration it decreases absorption of tetracyclines and bisphosphonates.
- Additive neuromuscular blocking effects with aminoglycosides, digitalis glycosides.
- Additive effects with nifedipine and CNS depressants.

Adverse Reactions:

- Oral: GI irritation, watery diarrhoea.
- Parenteral: Hypomagnesaemia characterised by nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, slurred speech, double vision, bradycardia, muscle weakness.
- Hypocalcaemia
- Paralytic ileus.

Different Magnesium supplements:

The one of the most popular types of magnesium supplements and easily absorbed by your body is magnesium citrate. The main use of magnesium citrate is to raise magnesium levels and treat constipation.

Magnesium glycinate has an easy absorption and may have calming properties. It helps in reducing anxiety, depression, stress, and insomnia.

Magnesium malate is absorbed in the digestive tract and makes it a great option for replenishing your magnesium levels.

Magnesium L-threonate is frequently used for its potential brain benefits. It also helps in managing certain brain disorders, such as depression and age-related memory loss.

Magnesium taurate is the best form to manage high blood sugar and high blood pressure.

Magnesium chloride has an easy absorption orally and used to treat heartburn, constipation, and low magnesium levels.

Magnesium oxide is often used to alleviate digestive complaints like heartburn and constipation. It is not a good choice for those who need to raise their magnesium levels as the body does not absorb it well.

7. Selenium

Selenium is obtained from the diet (i.e. fish, meat and cereals) & is an essential trace element. It affects the severity of a number of viral diseases.

Mechanism of action:

Selenium is an important element in both optimal innate and adaptive immune response. The T helper lymphocytes, cytotoxic T and NK cells, and macrophage phagocytosis are stimulated by selenium.

Selenium deficiency can cause an impairment of the host's immune system and mutation of benign variants of RNA viruses to virulence. Selenium has the potential to prevent and control RNA viruses by amplifying the signaling functions of TLR7.

Selenium improves immunity and reduces inflammation. It boosts the synthesis of glutathione peroxidase(GPX) that protects neutrophils from oxidative stress.

The entrance of viruses is inhibited into healthy cells by Selenium and it abolishes their infectivity.

Selenium also reduces the formation of thrombosis in the blood vessels.

Dosage:

- Prophylactic and Therapeutic dose of 100–200 µg per day,

Indications:

- Prophylactic: In healthy individuals, Covid contacts and Covid suspects
- Therapeutic: In all confirmed cases of COVID-19 (asymptomatic, mild, moderate & severe)

Contraindications:

- Selenium poisoning or hypersensitivity to products containing selenium
- Pregnancy: the use of selenium in pregnant women has no data; human milk excretes selenium. No effects are anticipated in newborn/lactating infants at therapeutic doses. During lactation, selenium can be used. No adverse effects on fertility are expected in doses to correct selenium deficiency.

Drug interaction:

- Do not use selenium and drug eltrombopag simultaneously

- Selenium and high concentrations of ascorbic acid are generally incompatible (reduction of selenite to elemental selenium which is not soluble and not available as a nutritional source of selenium).

Adverse effects:

- Gastrointestinal upset.
- Selenium toxicity is caused by very high selenium dosages (above 850 μg daily). The signs include depression, nervousness, emotional instability, nausea, vomiting, and in some cases loss of hair and fingernails.

Published studies in COVID-19:

The COVID-19 inpatients (n = 27) have higher significance in surviving as compared to non survivors (n = 6) with selenium intake (selenium and SELENOP). The efficacy of selenium is explained by its role as an essential cofactor in a group of enzymes along with vitamin E works to reduce the formation of reactive oxygen species (ROS).

The adequate intracellular levels of the cofactor glutathione (GSH), reduced GSH is associated with senescence in several species including humans is dependent on the optimal function of the GPXs. There is a deficit of the active form of GSH in the individuals with chronic diseases including hypertension. Dyspnea associated with COVID-19 pneumonia is relieved by an administration of glutathione.

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Brand name of Medicines:

1. Antiviral

A.Hydroxychloroquine in India:

- HCQS 200mg Tab
- Hydroquin 200mg Tablet
- Bioquin 200 Mg Tablet 10s
- RHQ 200 Mg Tablet 10s
- Hqtor 200mg Tablet 10s
- Qdmrd 200mg Tablet 10s
- Winflam 200 Mg Tablet 10s

B. Favipiravir in India:

- Tab FabiFlu 200mg or 400 mg
- Tab PiFLU
- Tab Favenza
- Tab Faviton 400

- Tab Xaravir
- Tab Favilow 200 mg tablets
- Tab Avigan (Favipiravir) 200 mg tablets
- Tab Alfluenza
- Tab Covihalt 200mg
- Tab Vergiflu

C. Lopinavir/ritonavir combination in India:

- Lopimune Tablet
- Ritomax L Forte Capsules
- Ritocom
- Hivus LR Tablet
- Emletra Tablet
- Aluvia Tablet

D. Remdesivir in India:

- Covifor 100 mg vial injectable
- Cipremi 100 mg or 200 mg vial injectable/ 200 mg tablet
- Ramdac 100 mg lyophilized injection
- Desremtm 200 mg IV
- Redyx

2. Antibiotics:
A. Azithromycin in India:

- Tab Azal 500mg
- Tab Azee 500mg
- Tab Azibact 500mg
- Tab Azimax 500mg
- Tab Azi-4-U 500mg
- Tab Azicor 500mg
- Tab Azithral 500mg

B.Cephalosporins in India:
Cefuroxime:

- Cefadur 500 Mg Tablet 10s
- Oratil-500 Tab 6s
- Furobid 500mg Tablet 4s
- Cefasyn 500 Mg Tablet 4s

- Novacef 500 Mg Tablet 4s
- Cefadur CA 500 Mg Injection
- Covatil 500mg Tablet 6s
- Omnixim 500 Mg Tablet 4s
- Cefadur CA 500 Mg Tablet 4s

Ceftriaxone:

- Monocef (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Monotax (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Odicef (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Xone (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Oframax (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Hetexone (250 mg, 500 mg, 1 gm, 2 gm injectable)
- Maczone (250 mg, 500 mg, 1 gm, 2 gm injectable)

Cefaperazone:

- 3a-Zone VIAL (Cefoperazone 500 mg, Sulbactam 500 mg)
- 3Cef Novo 1.5 VIAL (Cefeperazone Na 1000mg, Sulbactum 500mg)
- Acmetum VIAL (Cefoperazone 500 mg, Sulbactam 500 mg)
- Alzone-S POWD (Cefoperazone 0.5 g, sulbactam 0.5 g.)
- Apozone-S VIAL (Cefoperazone 500 mg, Sulbactam 500 mg)
- 3 Cef Novo 375 (cefeperazone Na 250mg, Sulbactum 125mg)

C. Doxycycline in India:

- Cap Acnedox-LB 100 mg
- Cap Apidox 100mg
- Tab Avidox-LB 100mg
- Tab Biodoxi 100mg
- Tab Ceedox 100mg
- Cap Dedoxyn 100mg
- Cap Codox 100mg
- Tab Dobid 100mg
- Cap Dox-M 100mg
- Tab Doxy

D. Sepsivac in India:

- SEPSIVAC INJ 0.1ml

E. Meropenem in India:

- Meros 1 gm injection
- Meromac 1 gm injection
- Eupen 500 mg injection
- Merotop 500 injection
- Merocrit 1 g vial
- Merotrol 1 g vial
- Aripnem 1000 mg vial

F. Piptaz (Piperacillin with Tazobactam) in India:

- Alzo in (Piperacillin 1 gm, Tazobactam 125 mg)
- Biopiper Tz inj (Piperacillin 4 gm, Tazobactam 0.5 gm)
- Durataz inj (Piperacillin 4 gm, Tazobactam 0.5 gm)
- Pipmax inj (Piperacillin 4 gm, Tazobactam 0.5 gm)
- Pip son inj (Piperacillin 1 gm, Tazobactam 0.125 gm)
- Piptazone (Piperacillin 4 gm, Tazobactam 0.5 gm)
- Piptal (Piperacillin 2 gm, Tazobactam 0.25 gm)
- Piptaz inj (Piperacillin 4 gm, Tazobactam 0.5 gm)

G. Ivermectin in India:

- Tab Agimect 12mg
- Tab Averm plus 12mg
- Tab Elect DT 12mg
- Tab Imectin 12mg
- Tab Ivecop 12mg
- Tab Ivercid 12mg
- Tab Iverdis 12mg

3. IL-6 inhibitors

A.Tocilizumab in India:

- Actemra (Tocilizumab injection (80mg/ 4ml, 200mg/10ml, 400mg/20 ml vials).

B.Itolizumab in India::

- Tab Alzumab

4. Vitamins:

A.Vitamin C:

- Tab Limcee 500mg,
- Tab Cell-C 500mg
- Tab Swicee 500mg
- Tab Frutcee 500mg
- Tab Sukcee 500mg
- Ener C 1000mg
- Tab Nature's Velvet Vitamin C 1000mg
- Tab Ascor 1000mg
- Tab Prorac C 1000mg

B.Vitamin D

- Syp Depura 60 k
- Tab Fovit D3
- Tab Vitalcal 60,000IU
- Cap Calcitus D3
- Tab Hira D3 60,000 IU
- Tab Vitcol D3

C.Vitamin E

- Cap Benvite
- Cap Bio 3 SG
- Cap Bio E
- Cap Ecap 400 mg
- Cap Evion
- Cap Ecod (with omega FA)

D.Vitamin B:

- Cap Beplex- Zee
- Cap Becosules
- Cap Beclac Forte
- Cap Benfree
- Tab B complex forte
- Cap Alnerve
- Tab Balcobal
- Tab BetaCobal forte
- Tab Bigvin

- Tab Elmecob

E.Magnesium:

- Tab Ultra Magnesium
- Tab Magark 500 mg
- Tab Remmag
- Tab Magmaxx 400mg
- Tab Magvion
- Tab Magins 400mg

F.Zinc:

- Tab Zincovit 50mg
- Tab Zinconia 50mg
- Tab Zica 50mg
- Tab Zincari 50mg
- Tab Zincorg 50mg

G.Selenium:

- Cap Selfert 200mcg
- Tab selenium plus

5. Anticoagulants

A. Low molecular weight heparin in India:

- Axeparin injection (Enoxaparin 40 mg)
- Clexane injection (Enoxaparin 20 mg/ 0.2 ml)
- Enclex injection (Enoxaparin 40 mg/ 0.4 ml)
- Enoxacare (Enoxaparin 40 mg)
- Humparin (Enoxaparin 20 mg/40 mg)
- Lomonox(Enoxaparin 40 mg)
- Maxiparin (Enoxaparin 40 mg/60 mg)
- Oxprin (Enoxaparin 60 mg)

6. Anti Inflammatory

A.Corticosteroids in India:

- Medrol (4 gm Tablets, 8 mg Tablets, 16 mg Tablets, 24 mg Tablets, 32 mg Tablets)
- Orapred (15 mg/5 mL solution)

- Prelone (15 mg/5 mL solution)
- Pediapred (5 mg/5 mL solution)
- Wysolone (5 mg, 20 mg)
- Omnacortil (5 mg, 10 mg, 20 mg)
- Methpred (5 mg, 10 mg, 20 mg)
- Crotorax-hc cream (0.25% w/w, crotamiton 10% w/w)
- Cutisoft cream (1% w/w)
- daktacort gel gel (1% w/w, miconazole nitrate 2% w/w)
- LUMINOSA cream (1% w/w)
- Dexona 0.5MG TAB
- Decdak 4MG TAB
- Decmax 4MG TAB
- Dexam 4MG TAB

Section F

Futuristic Therapies

26 Vaccines

The twenty-first century has seen the unfolding of and epidemic of three previously unidentified coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and 2019 novel coronavirus (2019-nCoV, later officially named SARS-CoV-2) in late December, 2019. These belong to a family of viruses called Coronaviridae, which possess a positive-sense single-stranded RNA genome. These viruses are characterized by significant genetic variability and high recombination rate that allow them to be easily spread among humans and animals worldwide. This is the reason why numerous coronaviruses exist within human and animal populations without causing any life-threatening diseases. But, sometimes the genetic recombination of viruses within random intermediate hosts produces contagious strains that are highly pathogenic to humans. Though SARS-CoV-2 is genetically and structurally related to SARS-CoV, it is becoming increasingly clear that it has its individualized characteristics that contributed to the fast spread around the globe. Since there is currently no effective treatment available for coronavirus infections, development of vaccines and therapeutic drugs to control the damage are of the utmost priority, as it is not only affecting the healthcare system, but also has an impact on the global economy. Even if we have undergone a huge leap in understanding of coronaviruses after two precedents, there is still scarcity of the successful proposals of treatment and epidemiological control.

Vaccine development efforts

In the last 10 years, the scientists and the vaccine producing industry have been expected to give rapid solutions to epidemics including Ebola, Zika, H1N1

influenza, and now SARS-CoV-2. The rapid and large scale production of an H1N1 influenza vaccine was possible only because influenza-vaccine technology was well developed and key regulators had previously been decided.

The plentiful publications from January 2020 to December 2020 shows the rigorous scientific effort to address molecular mechanisms as well as therapeutic routes for treating COVID-19. More than 200 clinical trials are currently advancing to test all new and repurposed compounds against SARS-CoV-2. However, in general, developing a novel vaccine is an extensive and a costly process. The rate of attrition is high, and it usually requires multiple candidates and multiple years to produce a licensed vaccine. Because of the cost and high failure rates, scientists typically undergo a linear sequence of steps, with multiple pauses for data analysis or to check manufacturing processes. To develop a new vaccine on an urgent basis needs a new pandemic paradigm, with a rapid start and many steps implemented in parallel before confirming a successful result of another step, hence it has a very high financial risk.

As soon as China announced that a novel coronavirus had been identified as the cause of the Wuhan outbreak, Coalition for Epidemic Preparedness Innovations (CEPI) contacted its partners that were developing MERS vaccines or working on novel platforms. With the potential for further financial support, they and others began vaccine development as soon as the first gene sequence was posted, and development is proceeding quickly. Approximately 8 vaccine candidates are receiving funding from the Coalition for Epidemic Preparedness Innovations (CEPI).

Vaccine

A vaccine is a biological preparation designed to protect humans from viral and bacterial infections. Vaccines stimulate the production of antibodies inside the human body before disease generation, in the same manner as antibodies are produced after the individuals are exposed to the disease pathogen [1].

The development of a vaccine guarantees a more secure, durable strategy to prevent COVID-19 outbreaks in the future. With the sequencing of the SARS-CoV-2 genome, various nucleic acid-based vaccine candidates have come forward and has proposed formulations, mostly based on the S protein-coding sequence.

Types of Vaccines

I. Nucleic acid vaccines

   A. RNA vaccines- Pfizer and BioNtech, Moderna, Curevac

   B. DNA vaccines- Inovio Pharmaceuticals, CanSino Biological, and Beijing Institute of Biotechnology CanSino Biological.

II. Vector vaccines- Oxford university and AstraZeneca (Serum Institute of India), Johnson & Johnson's vaccine arm Janssen Pharmaceuticals

III. Subunit and virus-like particles vaccines- The University of Queensland in collaboration with GSK29 and Dynavax30, Novavax

IV. Inactivated vaccines and Live Attenuated Vaccines- Bharat Biotech and ICMR, Sinovac, University of Hong Kong

V. Others- Shenzhen Geno-Immune Medical Institute

I. Nucleic acid vaccines

   A. RNA vaccines

In the first few days of January 2020, soon after the spread of COVID-19 pneumonia, the genome of SARS-CoV-2 was identified and sequenced. The advantages of using mRNA vaccines, when compared to more conventional attenuated or inactivated vaccines, is that these vaccines do not contain infectious material and are easier to develop and manufacture [2].

Leading RNA vaccine developers-

- **Pfizer and BioNtech**

On 11th December 2020, the US FDA authorised the emergency use of the mRNA vaccine, BNT 162b2 in individuals 16 years and older. BNT 162b2 is a lipid nanoparticle-formulated, nucleoside modified RNA vaccine encoding a prefusion stabilised and membrane anchored SARS-CoV-2 spike protein. Earlier, in April 2020, Pfizer and BioNtech had announced their collaboration for development of the mRNA-based vaccine for use initially in the U.S and Europe and then subsequently to support global supply by scaling up manufacturing capacity.

The U.S. phase 1/2 randomized, placebo-controlled, observer-blinded study that included healthy adults aged 18-55 years showed that their vaccine candidate demonstrated tolerability and immunogenicity [3]. Based on the preliminary data together with additional preclinical data, the two companies progressed to a large, global Phase 2b/3 safety and efficacy trial in July 2020 and in November, 2020, Phase 3 study results showed that their vaccine candidate, BNT162b2 met all the primary efficacy endpoints and there were no serious, vaccine related safety concerns [4].

Moderna, inc.

On 18 December, the US Food and Drug Administration (FDA) granted emergency use approval to the vaccine made by Moderna, Massachusetts. Moderna, Inc. is a US company and in collaboration with National Institute of Allergy and Infectious Diseases NIAID, has developed an mRNA lipid-nanoparticle–based vaccine. Moderna's sequence for the vaccine candidate is called mRNA-1273. It was first identified in January 2020 and contains a genetic code for the SARS-CoV-2 spike protein in a way that the mRNA sequence prompts cells to start producing the antigenic SARS-CoV-2 spike protein once administered, resulting in an immune response.

The route of administration is intramuscular injection to human bodies, and once administered it is expected to elicit an anti-viral response specifically toward the spike protein of SARS-CoV-2.

Most of the conventional vaccines are either made from inactivated pathogen or small subunits of live pathogen, but synthesis of the lipid nanoparticle-encapsulated mRNA vaccine does not need the virus. Therefore, it is fairly safe. Clinical trials began in March 2020, and approximately 45 individuals were enrolled over the course of 6 weeks for an open-label trial based in Seattle, Washington [5]. The phase 3 Coronavirus Efficacy (COVE) trial was later launched in July 2020 to assess its safety and efficacy in preventing SARS-CoV-2 infection. The vaccine was found to be 94% effective at preventing symptomatic COVID-19. The data and safety monitoring board reported that the vaccine met the prespecified efficacy criteria. Mild local reactions to the vaccine were noted. Moderate to severe systemic side effects including fatigue, myalgia, arthralgia, and headache were noted in 50% of the participants after the second dose. But, these were transient and resolved in most participants by day 2 without any sequelae [6].

- **Curevac, Inc.**

A Phase 2b/3 HERALD study was initiated by CureVac AG in December 2020. The trial assesses CureVac's COVID-19 Vaccine Candidate, CVnCoV, in two parts, an initial Phase 2b trial to further characterize the safety, reactogenicity and immunogenicity; and a Phase 3 trial to assess its efficacy. More than 35,000 participants will be included in the HERALD study at multiple sites in Europe and Latin America. Curevac announced the initiation of Phase 3 trial on 22nd December 2020.

CureVac AG, is a pharmaceutical company whose head office is situated in Germany. It focuses on developing mRNA-based vaccines and therapeutics and has received funding from CEPI in 2019 to make a mobile unit for rapid mRNA production for lipid-nanoparticle formulated mRNA vaccine candidates, possibly at the site of an outbreak [7].

It has been reported that the members of the Trump administration and the European UnionNews have approached CureVac executives to purchase vaccines, but it also brings to light the issues of ensuring impartial supply of vaccines once it becomes available for clinical use.

B. DNA vaccines

Compared to conventional vaccines, genetic vaccines require lower costs of production and easier ways of purification. The simple structure of nucleic acids also obviates the risk of incorrect folding, which could occur in recombinant protein-based vaccines.

While DNA vaccines have certain advantages, such as optimal development speeds and thermostability, past trials have shown that producing sufficient immunogenicity can be a challenge.

Leading DNA vaccine developers:

- **Inovio Pharmaceuticals (INO-4800)**

INO-4800 is a DNA vaccine candidate created by Inovio Pharmaceuticals, a US-based pharmaceutical company. It can be administered intradermally. Administration of this vaccine candidate requires the use of an electroporation device called CELLECTRA. It uses a small electrical current to make the dermal layers more permeable and thus warrants proper entry and incorporation of the DNA molecule into the cell. On April 6, 2020, Inovio Pharmaceuticals

announced that the U.S. FDA had approved its Investigational New Drug application. The trial enrolled up to 40 healthy adults in Philadelphia, PA, and Kansas City, MO.19 The company also received support from the Bill and Melinda Gates Foundation to accelerate the development and production of the electroporation device. Preliminary results demonstrated excellent safety and tolerability in the 38 enrolled subjects [8]. On November 16, 2020, the FDA approved Phase 2/3 clinical trial of its COVID-19 vaccine candidate. The Phase 2 segment of the trial will evaluate the safety, tolerability, and immunogenicity of INO-4800 in 2-doses (1.0 mg or 2.0 mg) to confirm the more appropriate dose for three age groups (18-50 years, 51-64 years and 65 years and above) followed by a Phase 3 evaluation of efficacy.

Like Moderna's mRNA-1273, INO-4800 is also a genetic vaccine that can be injected into human cells and translated into proteins to obtain immune responses. This consists of plasmid DNA that, upon administration, prompts human cells to produce the antigenic SARS-CoV-2 spike protein, similar to the development of other CEPI-funded Lassa and MERS experimental vaccines by Inovio.

II. Vector vaccines

Leading vector vaccine developers:

- Oxford university and AstraZeneca (ChAdOx1 nCoV-19) (Serum Institute of India)

This vaccine is created by the University of Oxford. Oxford University has partnered with AstraZeneca for further development of ChAdOx1 nCoV-19 vaccine, previously called AZD1222. CEPI has funded this group to develop vaccines against a variety of emerging diseases, including MERS, in the past. The vaccine uses an adenovirus that affects chimpanzees. A balanced Th1/Th2 humoral and cellular immune response was elicited in rhesus macaques after administering ChAdOx1 nCoV-19 (prime-only and prime-boost regimen) using intramuscular injection with 2.5 x 10 (hyphen 10) ChAdOx1 nCoV-19 virus particles. Significant reduction in the viral load in bronchoalveolar lavage fluid and lower respiratory tract tissue of vaccinated rhesus macaques was observed when compared with control animals. Also, vaccinated animals did not develop pneumonia. But, no significant difference in nasal shedding between vaccinated and control animals was seen.

Phase I/II trial with 1,077 healthy adult participants, aged 18-55 years showed

that the vaccine was well tolerated and generated robust immune responses. 4 late-stage Phase II/III blinded, randomised, controlled trials across the UK, Brazil, and South Africa have demonstrated an acceptable safety and efficacy profile of the vaccine [9].

In a significant breakthrough, the vaccine has received approval for emergency use in the United Kingdom for individuals 18 years or older and with the first doses being available in the first quarter of the year 2021. Based on the clinical trials, the authorisation recommends two doses to be administered in an interval of 4 to 12 weeks.

This is composed of a non-replicating adenovirus vector and the genetic sequence of the S protein of SARS-CoV-2. It has been tested as immunogenic in mice, eliciting a robust humoral and cell-mediated response.

It is relatively safe in children and individuals with underlying diseases because of the non-replicating nature of adenovirus in the host. Besides, the adenovirus-based vectors are characterized by a broad range of tissue tropism that covers both respiratory and gastrointestinal epithelium, the two main sites that express the ACE-2 receptor of SARS-CoV-2. However, the possibility of dominant immunogenicity toward the vector genes rather than the transgenes should always be considered.

In India the vaccine is being manufactured by Serum Institute of India (Covishield).

- **CanSino Biological, Inc., and Beijing Institute of Biotechnology CanSino Biological, Inc.,**

A China-based company, has collaborated with the Beijing Institute of Biotechnology to develop a non-replicating viral vector vaccine and are set to begin phase III clinical trials, with 40,000 participants [10,11]. The Phase II trial that included 508 participants demonstrated safety and ability to trigger an immune response. In order to conduct the large-scale Phase 3 trial, CanSino Biologics is in talks with Russia, Brazil, Chile, and Saudi Arabia.

The vaccine candidate uses a nonreplicating adenovirus type 5 viral vector containing the gene encoding the antigenic SARSCoV-2 spike protein [12]. The viral vector delivers the spike protein gene into human cells, leading to production of the protein that is designed to trigger an immune response [13].

- **Johnson & Johnson's vaccine arm Janssen Pharmaceuticals**

CEPI announced its most recent support of a consortium led by the Institut Pasteur in Paris on March 19, 2020. It also included the University of Pittsburgh and Themis.5 The funding has supported the initial preclinical testing and manufacturing, as well as preliminary work for phase I studies. Phase I clinical trial of their vaccine candidate TMV-083 began in August 2020 in france. The trial is being conducted in Paris Public Hospital Network and partly in Belgium and will include 90 healthy volunteers that will receive two doses of the vaccine 28 days apart. The results are expected in 2021.

The vaccine candidate consists of a replicating measles viral vector. The same institute has designed SARS vaccine candidates using the human measles vector, and collaborator Themis has developed potential phase III Chikungunya and phase I Lassa fever candidates using CEPI funding in the past [14].

III. Subunit and virus-like particles vaccines

Leading subunit and virus-like particles vaccines developers:

- **The University of Queensland in collaboration with GSK29 and Dynavax30** is developing a subunit vaccine consisting of a SARSCoV-2 spike protein stabilized with a protein "molecular clamp." The recombinant viral proteins are stabilized in their pre-fusion form. The molecular clamp procedure utilizes an antigenic protein that is shaped in such a way that it "clamps" onto virus protein and helps trigger an immune response. GSK in a separate partnership with Clover Biopharmaceuticals, based in China, announced the start of Phase-1 trial of its vaccine candidate on 150 adults from the healthy and high-risk categories. The vaccine is a subunit vaccine with its pandemic adjuvant system and an S-trimer protein that resembles the SARS-CoV-2 spike protein [15].

Molecular clamp vaccines have proved their capacity to induce the production of neutralizing antibodies in the past as well, when applied to influenza virus and Ebola virus. They were also reported to be potent after two weeks at 37 °C.

- **Novavax, Inc.,** a U.S-based company, has produced a nanoparticle-based vaccine using antigens derived from the coronavirus S protein. Phase 1-2 trial results showed that the vaccine appeared to be safe and it elicited immune responses. The Matrix-M1 adjuvant induced functional immunity and CD4+ T-cell responses in older adults, including those with coexisting conditions,

which is a population at risk for severe COVID-19 disease [16]. Novavax has begun enrolling approximately 30,000 adult volunteers for Phase 3, randomized, placebo-controlled trials being conducted at approximately 115 sites in the US and Mexico. The vaccine includes a recombinant SARS-CoV-2 spike protein and the company's Matrix-M saponin-based adjuvant. This adjuvant is a mixture of saponin and lipid molecules which induces the migration of antigen-presenting cells to the site of administration. They can be used as an alternative strategy to incorporate antigens, because through encapsulation or covalent functionalization, nanoparticles can be conjugated with antigenic epitopes, imitate viruses and induce an antigen-specific lymphocyte proliferation as well as cytokine production.

It is a mucosal vaccination which can be administered through intranasal or oral spray. It not only stimulates immune reactions at the mucosal surface, but also induces systemic responses. Hence they have the potential to protect us against respiratory viruses that cause systemic symptoms.

Same as various other institutes listed above, Novavax, Inc., has also participated in the research to produce vaccines against MERS and SARS.

IV. Inactivated vaccines and Live Attenuated Vaccines

Leading Inactivated vaccines and Live Attenuated Vaccines developers

- Bharat Biotech and ICMR (COVAXIN):

COVAXIN, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, vaccine is an inactivated whole-virion vaccine. The vaccine received DCGI approval on Jan 2, 2021 for restricted use. The trials took place across India from July, 2020. Phase I clinical trials were done on 375 volunteers at 12 medical institutes across the country. The trials showed long-term antibody and T- cell (immune) memory responses three months after the shot in phase 1 volunteers and tolerable safety outcomes in Phase 2 study. In Karnataka, phase 3 trials showed an average efficacy of 60-70 %. Covaxin is still in Phase 3 and has received restricted approval.

- Sinovac

Inactivated vaccines are made non-infectious by physical or chemical approaches. These have several advantages; they present with multiple viral

proteins for immune recognition, have stable expression of antigenic epitopes, and can be produced in large quantities. Sinovac has received authorization in China and Indonesia. The vaccine has entered phase 3 clinical trials. Phase 2 trials showed that the vaccine was well tolerated and immunogenic in healthy adults.

- **University of Hong Kong**

On March 18, 2020, CEPI announced it was providing funding to the State Key laboratory for Emerging Infectious Diseases of the University of Hong Kong to go forward with the preclinical testing. The vaccine candidate has a live attenuated influenza virus vaccine strain that can exhibit an antigenic element of the SARS-CoV receptor binding domain on its surface, to induce immunogenicity against the SARS-CoV-2 virus. On September 9, 2020, the University of Hong Kong announced that the first ever nasal spray COVID-19 vaccine received approval by China's National Medical Products Administration for clinical trials in humans.

V. Others

- **Shenzhen Geno-Immune Medical Institute (Pathogen-Specific Artificial Antigen-Presenting Cells)**

Based on the knowledge that antigen-specific T cells are able to eradicate cancer cells as well as viral infections, by promoting the generation of large amounts of T cells with viral antigen specificity in a timely manner may help us withstand the invasion of SARS-CoV-2.

Efficient methods to produce massive amounts of T cells include appropriate antigen-presenting cells that can activate effector T cells, and the differentiation and proliferation of corresponding effector, cytotoxic T cells. Hence, the genetically modified artificial antigen-presenting cells (aAPCs) that express the conserved domains of the viral structural proteins delivered by lentivirus vectors are supposed to evoke the naïve T cells in the human body and lead to differentiation and proliferation.

Phase 1/2 trials are now evaluating the safety and immunogenicity of aAPCs alone and in combination with antigen-specific cytotoxic T cells (NCT04299724, NCT04276896).

Each vaccine platform has its own list of advantages and disadvantages. For instance, nucleic acid vaccines can be easier to design, but DNA vaccines may

not be as immunogenic, and mRNA vaccines may be more unstable. Additionally, viral vector vaccines and subunit vaccines generally exhibit higher safety profiles and are more immunogenic, but viral vector vaccines may have reduced efficacy due to preexisting immunity to the vector, and subunit vaccines may be too expensive.

Operation **Warp Speed** is a public–private partnership, initiated by the Trump administration, to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. Operation Warp Speed was introduced in early April 2020. It aims to deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021. OWS is a partnership among components of the Department of Health and Human Services (HHS), including the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD). HHS plans for a tiered approach to vaccine distribution. The system would likely prioritize groups at greatest risk of severe complications from Covid-19 and key workers.

Role of India in developing vaccine against COVID-19:

- **Covaxin (Bharat Biotech):**

India's Bharat Biotech is a pioneering biotechnology company known for its world-class research and development and manufacturing capabilities to deliver affordable, safe and high-quality vaccines and bio-therapeutics that help people prevail over diseases since 20 years. Covaxin, Bharat Biotech (with ICMR) COVID-19 vaccine candidate is in Phase 3 clinical trial with 26000 participants across India making it India's first and largest efficacy trial ever undertaken. It became the first indegenous vaccine to have received restricted approval. Vaccination drive using the vaccine has already begun in India. Bharat Biotech has also applied to conduct trials in Bangladesh for its coronavirus vaccine. If allowed to go ahead, this would be the first trial of any coronavirus vaccine in Bangladesh and could give the densely-populated country of more than 160 million faster access to the shot for mass use.

Bharat Biotech along with Washington UniversitySchool of Medicine, St Louis has been actively involved in development of an intranasal vaccine for Covid 19 -BBV154 which involves use of novel Chimpanzee adenovirus. They are about to initiate the Phase-1 trials for the same.

- **Covishield (Serum Institute of India)**

Covishield vaccine is manufactured by the Pune-based Serum Institute of India in collaboration with the University of Oxford and AstraZeneca and has been described earlier in the chapter.

Serum Institute of India is the largest vaccine manufacturer in the world. As the pandemic began to unfold, Serum Institute of India struck a deal with the University of Oxford and AstraZeneca to secure coronavirus vaccine licenses. In early May 2020, Serum Institute received a 1-millilitre vial from Oxford, England, containing the cellular material for the vaccine, which started off the work on mass production of the vaccine.

The two Indian approved vaccines have so far approached half a million number of vaccinations in three days since January 16th 2021.

- **ZyCoV-D**

ZyCoV-D is a DNA-plasmid based vaccine. Preclinical trials were being done at National Institute of Virology (NIV), Pune to fast track the process of vaccine production. The Ahmedabad based Zydus Cadila plasmid DNA vaccine candidate recieved clearance for Phase 3 trials. If approved, it will be the second indegenous vaccine.

Current Status of Vaccines against SARS CoV-2

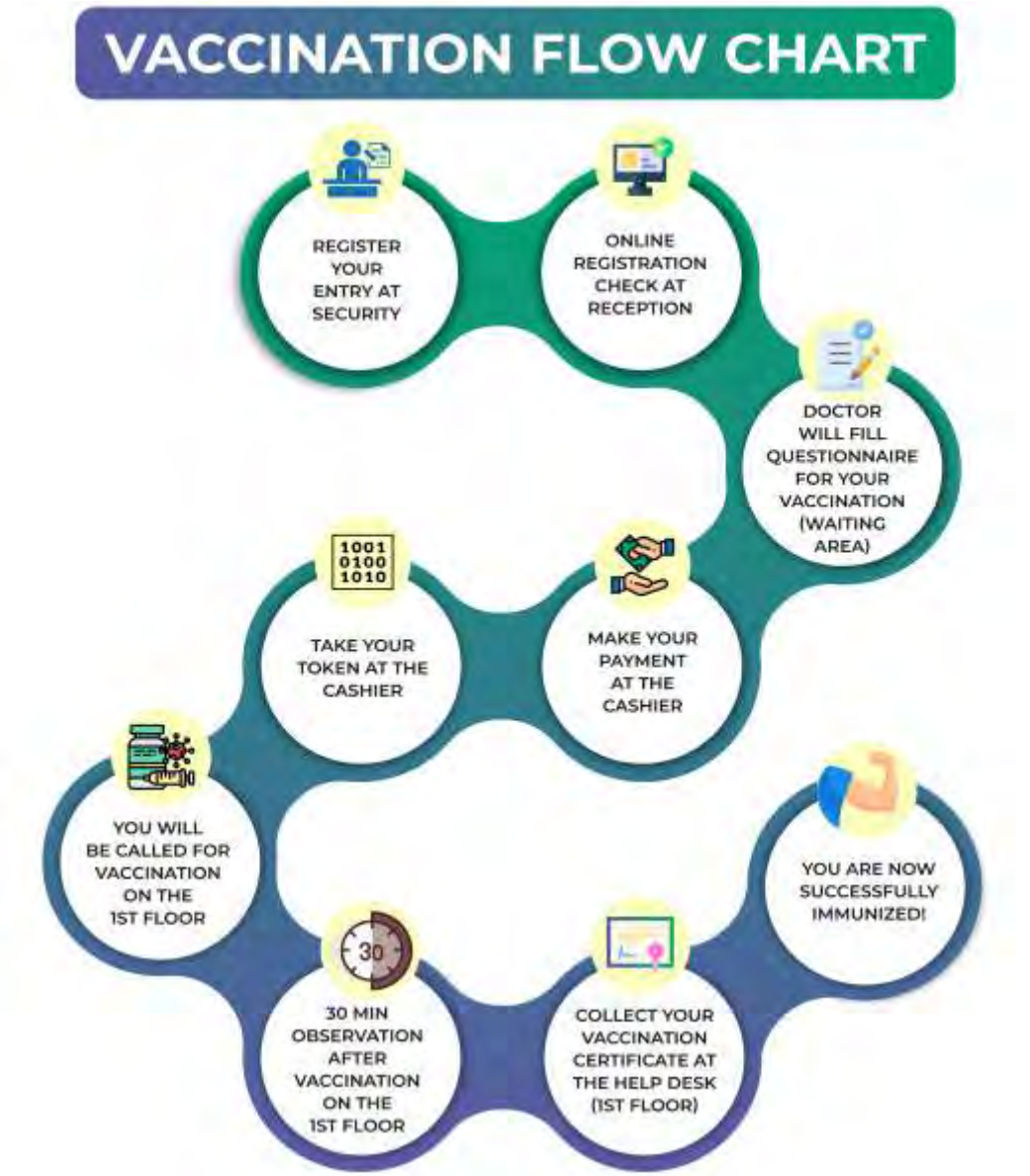
A. India

In a major breakthrough move, India recently approved two vaccines, the Oxford Covid-19 vaccine Covishield, manufactured by the Serum Institute of India, and Bharat Biotech's Covaxin for emergency use in the country.

Union Health Minister Dr Harsh Vardhan revealed that 400-500 million doses were estimated to be made available for around 30 crore people in India by July-August 2021.

On January 16th, 2021 the Prime Minister of India, launched one of the world's biggest vaccine drive in India. The drive aims at inoculating 3 crore health and other frontline workers first (Phase 1) using Covishield and Covaxin followed by 27 crore older than 50 or considered at high-risk. The aim is to inoculate 3,00,000 people on the first day with the first of the two doses of one of the two approved vaccines. The rest of the population will be inoculated subsequently.

Following clearance, the Zydus-Cadila and Bharat Biotech would also add around 40 crore doses annually. Inoculating 60% of India's population (80 crore) would be enough to develop herd immunity. Herd immunity is a form of indirect immunity that occurs when a sufficient percentage of the population has acquired immunity against an infection. The Indian Government also plans to provide Serum Institute's Covishield to Nepal and Bangladesh. Government of India has approved NeuroGen Brain & Spine Institute, Navi Mumbai for administration of Covid Vaccine.



B. Worldwide

Although vaccines take an average of 10 years to develop, the worldwide endeavour to develop and manufacture a safe and effective COVID-19 vaccine has borne fruit with a few vaccines being authorised and approved around the globe [Table. 1].

Leading vaccines	Vaccine Developer	Vaccine Type	Status
Comirnaty (BNT162b2)	Pfizer-BioNTech	mRNA	Approved in Saudi Arabia. Emergency use in U.S., E.U., Singapore, Oman, Switzerland, Kuwait
Moderna COVID-19 Vaccine (mRNA-1273)	Moderna	mRNA	Emergency use in the U.S., E.U.
Sputnik V	Gamaleya	Ad26, Ad5	Early use in Russia. Emergency use in Belarus.
COVID-19 Vaccine AstraZeneca (AZD1222)	Oxford-AstraZeneca	ChAdOx1	Emergency use in Britain, India
Convidicea (Ad5-nCoV)	CanSino	Ad5	Limited use in China.

JNJ-78436735 (formerly Ad26.COV2.S)	Johnson & Johnson	Non-replicati ng viral vector	Phase 3
NVX-CoV2373	Novavax	Subunit	Phase 3
BBIBP-CorV	Sinopharm	Inactivated	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
CoronaVac	Sinovac	Inactivated	Limited use in China, Indonesia. Emergency use in Brazil.
No name announced	Sinopharm-Wuhan	Inactivated	Limited use in China, U.A.E.
Covaxin	Bharat Biotech	Inactivated	Emergency use in India.

Table 1. Leading vaccines across the globe and their current status

Practical considerations of COVID-19 vaccines

Comirnaty (BNT162b2) by Pfizer has an efficacy of about 95% but requires freezer storage at-94° F or -70 ° C. This requires ultracold infrastructure for transporting and storing vaccines making it costly and difficult to vaccinate people in the lower and middle income countries. The Pfizer vaccine will be distributed in specially designed, temperature-controlled thermal shippers packed with dry ice to maintain recommended temperatures.

Moderna's vaccine, however, is stable at temperatures (-20° C) that can be achieved by standard freezers found in most pharmacies.

Indian vaccines, Covishield (AstraZeneca, AZD-1222), and Covaxin can also be stored, transported, and handled at normal refrigerated conditions of 20° C. This however, is a constraint especially with a large number of doses. Vaccines may lose potency when exposed to higher temperatures and re-cooling does not help. In India, a bulk of the vaccines will be distributed through the Centre's Universal Immunisation Programme (UIP) mechanism but the government

may also need to rope in private cold chain operators. The vast scale of India's UIP is supported by more than 27,000 functional cold chain points of which 750 are located at the district level and above and the rest are located below the district level. Cold chain logistics involves many moving parts, including cold storage facilities that store products to be transported, cooling systems to keep it at an appropriate temperature during all aspects of the supply chain such as storing and transporting. Gel packs are also often used for medical and pharmaceutical shipments. Besides the temperature control, there are issues concerning security also. Due to the initial unavailability of vaccines for everyone, there is a risk of counterfeiting, tampering and diversion. Security will be important and will have to be maintained not just at the manufacturing sites but also at vaccination sites.

Safety concerns

Allergic reaction to vaccination

Allergic reactions to vaccines are rarely attributed to the active vaccine itself as they might be caused due to excipients(inactive ingredients) such as egg protein, gelatin, formaldehyde, thimerosal, or neomycin, which contribute to specific IgE-mediated immediate reactions.

Before administration of any currently available COVID-19 vaccines, the individual'spast medical history should be assessed for any previous severe or mild allergic reactions to any cause and especially to the vaccine's components.

Individuals with common allergies to several medications, foods, inhalants, insect stings, and latex have the same chance to develop an allergic reaction to the COVID-19 vaccine. Those with a history of a severe allergic reaction due to any cause should be monitored for a 30-min observation period if vaccinated with the COVID-19 vaccine. Anyone with a history of immediate allergic reaction of any severity to any component of mRNA COVID-19 vaccines or to polyethylene glycol or polysorbate should not be vaccinated with the Pfizer-BioNTech or Moderna COVID-19 vaccine. Atopy increases the anaphylaxis risk 2-fold and is not associated to any specific groups of drugs.

The questions that physicians should have in mind are related to previous severe or mild allergic reactions and include the following:

- Mild allergic reactions, such as hives, nasal congestion, rash, scratchy throat, watery or itchy eyes to any injection, or orally and locally given substance.

- Severe allergic reactions, such as angioedema, cardiovascular collapse, includingKounis syndrome, cerebral manifestations, chest tightness, flushing, hives, laryngealedema, loss of consciousness, low blood pressure (anaphylactic shock), shortnessof breath, swelling of mouth, lips, tongue, throat, or wheezing to any oral, local orinjectable medication (intravenous, intramuscular, or subcutaneous).
- Severe allergic reaction to a previously injected vaccine.
- Severe allergic reaction to another substance acting as an allergen (e.g., food, venom, or latex)
- Severe allergic reaction to PEG or polysorbate.
- Patients with a history of severe allergic reactions to PEG or polysorbate should avoidthe current vaccination.
- Patients with a history of severe allergic reactions to other vaccinesor injected drugs shouldbe referred to an allergist for further investigation.
- Patients with alatex allergy should receive the vaccine in an absolutely latex-free environment.
- The rest of the patients with a history of allergic reactions, as defined above, shouldreceive the vaccine with a possibility of allergic reaction similar to the general population.

After authorisation or approval, vaccine safety monitoring systems observe for adverse events and/or possible side effects. This continuous monitoring can pick adverse events and enable decision making for any recommended changes that may be needed. Although Pfizer reported no serious adverse events during trials involving nearly 44,000 participants, the FDA and Centers for Disease Control and Prevention (CDC) panel earlier recommended people with a history of severe allergic reactions to avoid the Pfizer vaccine. People with allergic reactions to mRNA vaccine for other illnesses are advised to consult their doctors whether or not they should get a COVID vaccine. Of the 2,72,001 doses administered, six severe allergic reactions have been reported in the U.S. Scientists have postulated that the compound polyethylene glycol (PEG) which is part of the fatty envelope surrounding the mRNA may be responsible for the allergic reactions. People with allergic reactions to PEG and polysorbate are advised not to get the Pfizer vaccine. Besides these, four cases of Bell's palsy

were reported in people receiving the vaccine. Norway has administered at least one dose of the Pfizer vaccine to 33,000 people considered to be most at risk. Around 23 people passed away shortly after receiving the vaccine and after investigating the deaths, the Norwegian Institute of Public Health said that the COVID vaccines may be risky for the very old, terminally ill, and those with the most severe frailty since even relatively mild vaccine side effects can have serious consequences.

Similarly, a U.S. based doctor suffered a severe allergic reaction soon after being administered the Moderna vaccine. He began to feel dizzy soon after inoculation. CDC later however suggested that those with a history of reactions to vaccines or injectable drugs need not avoid the vaccination, but suggested that they be monitored for 30 minutes after getting the shot. The others are asked to wait for 15 minutes after the shot. The FDA is however, not clear about efficacy and safety in children younger than 16 years of age. More data is also needed to assess safety of both Pfizer and Moderna vaccines in pregnant and lactating women. Moderna vaccine is for people 18 years and older. The vaccine has begun testing in 12 to 17 year olds.

Five cases in the UK have reported an extremely rare form of blood clot occurring in conjunction with lowered platelets after being administered with the AstraZenica / Oxford vaccine. As a result, the Medicines and Healthcare products Regulatory Agency(MHRA), UK has issued an advisory as a precautionary measure for individuals taking this vaccine. Individuals experiencing headache for more than four days and/or bruising in locations other than the injection site should seek urgent medical assistance as this may occur possibly due to Venous Sinus Thrombosis or thrombocytopenia. VST describes the formation of a blood clot in the cerebral vein of the brain. Symptoms of which include headache, blurred vision, fainting or loss of consciousness. Whereas, thrombocytopenia describes when a person has a lowered number of platelets, which are cells that help the blood to clot. Ophthalmologists should also be aware of these side effects occurring due to vaccination such as headache (raised ICP), altered vision (transient visual obscurations, VF defects, red desaturation), horizontal double vision worse for distance than near, or worse to one side (false localising unilateral or Bilateral sixth nerve palsy) or disc swelling (raised ICP, inflammation). Specific enquiry about covid exposure and vaccination status, and dates thereof should be made and documented in the history. The MHRA points out that no causal link has been established, and that VST occurs in people who have not been vaccinated, and also occurs in people testing positive for covid. They emphasize that the

benefits far outweigh the risks.

India, likewise has an existing vaccine safety surveillance called the Adverse Events Following Immunisation (AEFI). The AEFI reported 447 cases of adverse events following the first two days of vaccination drive. Three of the cases required hospitalisation of which two are stable and one is under observation at AIIMS, Delhi. Two cases of severe AEFI were also reported after receiving a dose of Covaxin. Most other adverse events were minor and included fever, nausea, and headache. People with a history of allergies, fever, and bleeding disorders, on blood thinners, and those who are immunocompromised or on medication, pregnant, and breastfeeding women have been advised not to receive the vaccine by Covaxin manufacturer, Bharat Biotech. People with severe allergies to any ingredient of Serum Institute's Covishield (L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, Polysorbate 80, Ethanol, Sucrose, Disodium edetate dihydrate (EDTA)) or if a person had a severe allergic reaction after previous dose of the vaccine have been advised against the vaccine.

Frequently Asked Questions on Covid-19 & Covid vaccines:

Q. Is it possible to get positive RT-PCR test following COVID vaccination?
A. No.

Q. What to take for body ache and fever after vaccination?
A. A Paracetamol can be taken

Q. After how many days should the 2nd dose of the vaccine be taken?
A. 2nd dose of the vaccine should be taken between 28 and 42 days

Q. How long after the Covid vaccine do you get a positiveAntibody result?
A. Positive antibody in 40% by week 2, and over 90% by week 4.

Q. How long does immunity last after COVID19?
A. For those who recover from COVID19, immunity to the virus can last at least 8 months and maybe longer

Q. How long vaccine-induced immunity last?
A. We don't know as yet. Most of the trials have 2-3 months follow up data only, we need a longer follow-up

Q. What a positive antibody test means?
A. Different serological tests measure different types of antibodies. Most

commercial tests don't measure neutralisingantibodies.

Q. If you have a positive antibody test means you're immune to the virus?
A. For some infections, antibodies might protect against reinfection. For others, they may not prevent reinfection, but symptoms may be milder. In yet other cases, antibodies may provide no protection at all. Also, some test results may be "false positives."

Q. If you test negative for antibodies after >14 days of 2-doses of Covid vaccines, does it mean you are not protected?
A. No, absence of antibodies does not mean absence of protection. You may still have memory B cells & T cells responses that are not measured by routine lab tests.

Q. Is there any new study related to presence of antibodies& risk of infection with COVID19?
A. A recent study published in JAMA network shows that Individuals who are seropositive for SARSCoV2 based on commercial assays may be at decreased future risk of SARSCoV2 infection.

Q. Do current COVID vaccine protect against asymptomatic infection?
A. Yes, they do but how best we don't know for sure. Studies from Israel show that Pfizer vaccine provides a very high protection ~94% antigen asymptomatic infection. But we need more data

Q. Can we differentiate Flu from COVID19 based on first symptoms?
A. According to a new study, while influenza typically begins with a cough, the first symptom of COVID19 is fever.

Q. Are current generation of Covid vaccines effective against all new variants?
A. For UK B117 & Brazilian P1 variants, most vaccines are equally effective as with wild strain. Only marginal efficacy is lost. However, against SA B1351 variant, most vaccines are modestly efficacious.

Q. Is it true that current Covid vaccines are effective against serious disease even antigen SA variant?
A. Yes. Since T cells prevent severe illness & death, & most of the T cells functions remain intact even ag these variants.

Q. Is it ok to take 2 different brands of vaccines?

A. No. One should take both doses of the same brand of vaccine

Q. Is it safe for me to get a COVID19 vaccine if I would like to get pregnant?
A. Yes. If you are trying to become pregnant now or want to get pregnant in the future, you may receive a COVID-19 vaccine when one is available to you.

Q. I definitely had COVID19, but my antibody test result is negative. Are false-negative results possible?
A. Yes, but they are not common: just 3.7% of people who had mild or moderate COVID19 had a negative Ab test afterwards.

Most often this arises because the COVID occurred several months prior to the Ab test.

Q. Is it true that those already infected & seropositive, need only a single dose of covid vaccine?
A. Yes, many studies have shown the utility of a single dose, & futility of more doses in seropositive individuals.

Q. Do we have any immunocorrelate of protection for prevention of SARSCoV2 infection?
A. No. However, in NHP studies, it's seen that titers of NAbs ranging from 100-500 may provide sterilising immunity.

Q. Are the correlate of protection(CoP) against Covid disease and SARSCoV2 infection different?
A. Yes, in case of SARSCoV2 infection & vaccine studies, we measure NAbs as probable correlate. However, in Covid illness, the NAbs titers rise in regard with severity of disease. More severe disease ass with higher NAbs titers. Hence, NAbs are not protective.

Q. Then, what is the immune CoP against severe Covid?
A. It's believed that IgG Abs against prefusion Spike proteins & IgG Abs against Fusion Peptide serve as a definite CoP against severe Covid& death. Presence of these Abs offer protection against severe disease and death.

KLS Wellness Institute
&
NeuroGen Annexe
POWERING YOUR IMMUNITY

Questionnaire for COVID-19 Vaccination

Patient Name: _____ Age / Sex : _____ Date: _____

Contact No.: _____ Email: _____

Relative's Contact: _____ Address: _____

For Office Use

1st Dose ☐ 2nd Dose ☐ Date of last dose _____ Token No. _____

1. Do you have any comorbidities? Yes ☐ No ☐

Remarks if yes: _____

2. Do you have allergies to any vaccines, injections, medicines, food, etc.? Yes ☐ No ☐

Remarks if yes: _____

3. Have you had any vaccinations in last 15 days (COVID-19 vaccine and other vaccines should be spaced at least 14 days apart? Yes ☐ No ☐

Remarks if yes: _____

4. Do you have any active symptoms of COVID-19? Yes ☐ No ☐
(If yes),vaccination will be deferred for 8 weeks after recovery.

Remarks if yes: _____

5. Have you received SARS-COV-2 monoclonal antibodies or convalescent plasma? Yes ☐ No ☐
(If yes),vaccination will be deferred for 8 weeks after recovery.

6. Are you on any blood thinners eg. heparin, ecosprin, clopitab, warfarin, etc.? Yes ☐ No ☐

Remarks if yes: _____

7. Do you have any acute illness or history of hospitalization with or without ICU? Yes ☐ No ☐
(If yes),vaccination will be deferred for 8 weeks after recovery.

Remarks if yes: _____

8. Females : Are you pregnant? Yes ☐ No ☐

Are you breastfeeding? Yes ☐ No ☐

Last Menstrual Period: _____

9. Vitals - BP: _____ Pulse: _____

Temp.: _____ SpO_2: _____

Beneficiary Signature: _____ **Doctor Name & Sign:** _____

वुथवर लाभार्थ्यांना लस देण्यापुर्वी Vaccinator मार्फत विचारण्याचे प्रश्न/महत्वाच्या बाबी

१. वय - लाभार्थ्याचे वय १८ वर्षांपेक्षा जास्त असणे आवश्यक आहे.

२. मागील १५ दिवसापूर्वी आपण कोणती लस घेतली आहे का? (कोव्हिड १९ लस आणि इतर लसीमध्ये किमान १४ दिवसांचे अंतर असावे)

३. आपणास कोणत्या लसीची, इंजेक्शनची, गोळ्यांची, अन्नाची ॲलर्जी आहे का? (असल्यास, लस देण्यात येऊ नये)

४. महीला

a. शेवटचा पाळी कधी आली? (गरोदर मातांना लस देण्यात येऊ नये)

b. आपणाला लहान बाळ आहे का? हो/नाही

c. असल्यास, बाळाला अंगावरचे दुध पाजता का? (बाळाला अंगावरचे दुध पाजत असलेल्या मातांना लस देण्यात येऊ नये)

५. आपणास रक्त पातळ करण्यासाठी गोळ्या किंवा इंजेक्शन (उदा. Heparin) सुरु आहेत का? (असल्यास सदर लाभार्थ्यांना काळजीपुर्वक लस देण्यात यावी)

a. इंजेक्शनच्या जागी कापसाचा बोळा दाबून धरण्यास सांगावे.

b. १० मिनिटानंतर Vaccinator ने observation रुममध्ये जाऊन इंजेक्शनच्या जागी Bleeding होत नसल्याची खात्री करावी.

c. Bleeding होत असल्यास वैद्यकीय अधिका-यांशी संपर्क साधावा.

६. पुढील नमुद लाभार्थ्यांना लस देता येईल.

a. यापूर्वी ज्यांना कोव्हिड आजार झाला आहे आणि अथवा RT-PCR तपासणी पॉझिटीव्ह आहे.

b. Cardiac, neurological, pulmonary, metabolic, renal, malignancy असल्यास आणि कोणाला पूर्वीपासून आजार असल्यास

c. HIV पॉझिटीव्ह रुग्ण किंवा ज्या रुग्णांची एखादया आजारामुळे प्रतिकार शक्ती कमी आहे असे रुग्ण.

चार महत्वपूर्ण संदेश

१. आज आपणास कोरोनाची Covishield लस देण्यात आली आहे व ही लस आपले कोरोना आजारापासून संरक्षण करेल.

२. लस घेतल्यानंतरही कोरोना आजारापासून सुरक्षित राहण्याच्या पध्दती जसे की - मास्क लावणे, वारंवार हात धुणे आणि सहा फुटांचे शारीरीक अंतर ठेवणे बंधनकारक असेल.

३. पुढील डोसची तारीख, वेळ व ठिकाण आपणास आपल्या मोबाईलवर एस.एम.एस.(SMS) द्वारे कळविण्यात येईल. दुसरा डोस देखील Covishield या लसीचाच घेतला जाईल याबाबत दक्षता घ्यावी.

४. लसीकरणानंतर आपणास काही त्रास जाणवल्यास आपण आपल्या जवळच्या नागरी प्राथमिक आरोग्य केंद्र, वैद्यकीय अधिकारी यांच्याशी संपर्क साधावा.

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27 Ozone Therapy for COVID-19

We acknowledge Ozone Forum of India, Bisleri Charitable Trust, Dr. Mili Shah & Dr. Jignasha Captain for their contribution towards ozone treatment of Covid Patients.

What is ozone therapy?

Ozone therapy has been utilized and extensively studied as a treatment for various conditions for almost 150 years. During the first world war, doctors used topical application of ozone for infected wounds and discovered that alongwith treating infection, it also has hemodynamic and anti-inflammatory properties. Use of medical ozone is approved in 22 countries inclusing Germany, Russia, Italy, France, Hungary, Egypt, Britain, Romania, Poland, Bulgaria, Czech Republic, japan, Singapore, Mexico and 25 US states

Ozone is made by three oxygen atoms (O3) and Medical Ozone is a mixture of 0.5-5% ozone and 99.5-95% oxygen. It is highly soluble in water thus can immediately react with any soluble compounds and biomolecules present in biological fluids. It is a paradoxical oxidative agent which can stimulate endogenous antioxidant pathways, enhance energy and oxygen supply through blood to tissues and has anti-inflammatory properties which reduces inflammation. It also has germicidal and antiviral properties. Systemic Ozone can be administered via (a) Major and Minor autohemotherapy with ozonised blood (b) IV ozonised saline (c) Rectal insufflation.

(a)Autohemotherapy with ozonised blood: Autohemotherapy is a technique

that involves withdrawal of blood from the body and the reinjection of the same blood which is ozonated back into the body. The aim of the therapy is to enhance the immune system's ability to fight disease. Autohemotherapy is performed by either administering ozonated blood intravenously (Major AHT) or via intramuscular route (Minor AHT).

(b)IV ozonised saline: Use of ozonized saline solution (O3SS) procedure is not only effective and secure, but is much cheaper and easy to implement. It is a widespread practice in Russia and developed by the Russian school of ozone therapy in the city of Nizhny Novgorod (Volga Federal District). The method consists of prior saturation of the saline solution with a mixture of oxygen-ozone and its intravenous infusion to the patient.

(c)Rectal insufflation: Rectal Insufflation refers to introducing ozone into the body through the rectum. Rectal Ozone Insufflation is performed regularly in clinics worldwide, and can also be performed at home. It is painless and a minimally invasive method of administration which is also less time consuming as compared to other methods

Mechanism of action of Ozone therapy:

Underlying mechanism of ozone therapy involves inactivation of viruses, oxidation of bacteria, yeast, parasites, cancer cells and has powerful germicidal effect. It normalizes hormone and enzyme production, improves blood circulation, increases tissue oxygenation, improves immunity and overall metabolism and energy, has antiinflammatory and analgesic effect, regulates oxidative stress, improves RBC rheology and microcirculation and improves healing. Ozone therapy when administered systemically it shows beneficial effects such as modulating activity of inflammation, along with oxygenation it is also helpful in induction of endogenous production of interferons, signalling molecules that help to restructure immunity and fight various types of viruses. Which is why, administering it at an early stage along with main line treatment is key for faster results

Anti Inflammatory effects:

Ozone, in therapeutic dosages, activates nuclear factor erythroid 2-related factor 2 (Nrf2) which inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. NF-κB pathway induces the production of pro-inflammatory interleukins (TNFα, IFNγ, IL1β, IL6, IL8) in inflamed tissues.

Thus, blocking the pathway downregulates the release of proinflammatory cytokines and stimulates anti-inflammatory cytokines such as IL-4 and IL-10.

Antiviral and germicidal effect

Ozone damages the viral capsid and upsets the reproductive cycle by disrupting the virus-to-cell contact with peroxidation. The weak enzyme coatings on cells which make them vulnerable to invasion by viruses make them susceptible to oxidation and elimination from the body, which then replaces them with healthy cells. Ozone administration prevents entry of the virus in host cells. Ozone also has a potential bactericidal potential and may prevent secondary infection in patients.

Antioxidant effects:

Ozone modulates cytotoxity and oxidative stress and exhibits cytoprotective effect by stimulating endogenous antioxidant pathways. It enhances antioxidant enzymes like superoxide dismutase, glutathione peroxidase, catalase, etc which controls the cellular damage.

Improved oxygenation:

Ozone therapy improves oxygenation and blood circulation in the ischemic tissues by improving oxygen metabolism. It improves blood cell glycolysis by stimulating 2,3 diphosphoglycerate which in turn increases the amount of oxygen released into the tissues. It also enhances production of ATP by influencing Kreb's cycle to increase oxidative carboxylation of pyruvate. Effect of ozone administration on energy metabolism can therefore potentially reverse hypoxia.

Use of ozone for treatment of COVID-19

Ozone therapy has been extensively employed for treating various chronic diseases like infected wounds, circulatory disorders, geriatric conditions, macular degeneration, viral diseases, rheumatism/arthritis, cancer, severe acute respiratory syndrome and AIDS. Ozone may help improve the symptoms of COVID-19 by modulating pro-inflammatory cytokines and improving tissue oxygenation. It boosts innate antiviral responses. The most promising mechanism of ozone is modulation of the "cytokines storm" through the balanced regulation of the Nrf2/NF-κB pathway. Published studies have shown positive results of ozone therapy in COVID-19. Patients have shown

remarkable decrease in biomarkers like C- Reactive Protein (CRP), Interleukin 6 (IL6), fibrinogen, Lactate Dehydrogenase (LDH) and D-dimer. The oxygenation, respiratory indices and gas exchange markers also showed improvement post treatment. Clinical symptoms like dyspnea, weakness, fever also showed significant improvements. None of the studies reported any major irreversible adverse effects of ozone therapy. In a recently published randomized controlled clinical study by the Ozone Forum of India, it was noted that the ozone group showed clinically significant improvement in all the parameters tested compared to the group that received only standard treatment. Statistical significance was observed in RT-PCR negative reaction ($P = 0.01$), changes in clinical symptoms ($P < 0.05$) and requirement for Intensive care ($P < 0.05$). No adverse events were reported in the ozone group, as against 2 deaths reported in standard treatment group.

Main contraindications for ozone therapy are hyperthyroidism, active bleeding, G6PD deficiency, thromocytopenia.

Ozone as Prophylaxis HCW

Ozone administration may also play a role in preventing the SARS-CoV-2 infection. A study was conducted on healthcare workers at NeuroGen Brain and Spine Institute, a dedicated covid hospital, wherein 64 received the ozone prophylaxis and 171 did not. The incidence of COVID-19 was significantly lesser in the group that received ozone prophylaxis as compared to those who did not. Benefit was seen irrespective of the risk of exposure. No major adverse events were noted.. Our study elucidates the beneficial effect of IV ozonised saline as prophylaxis in reducing incidence of COVID-19 in HCWs without any major, irreversible adverse events.

Side effects of Ozone therapy

- Accidental inhalation may lead to symptoms like burning of eyes, coughing, nausea or vomiting, or mild headache. It can irritate the lungs and cause fluid buildup that makes it difficult to breathe.
- Rectal administration of ozone may rarely give mild discomfort, a feeling of passing gas, gurgling, or mild cramps which is temporary.
- Sometimes a patient may have a Herxheimer (Healing) Reaction (detoxification & healing symptoms) during which a patient may feel flu-like symptoms or feel a bit worse temporarily; this improves on continuation of

therapy. This is not an Ozone side effect but a natural healing process seen in other modalities as well.

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28 Stem Cell Therapy for COVID-19

Stem cell therapy is an evolving branch of modern medicine. It involves use of stem cells for therapeutic purposes owing to their immunomodulatory and regenerative properties. It has the potential to repair the damaged tissues by restoring or replacing lost or damaged cells with healthy ones.

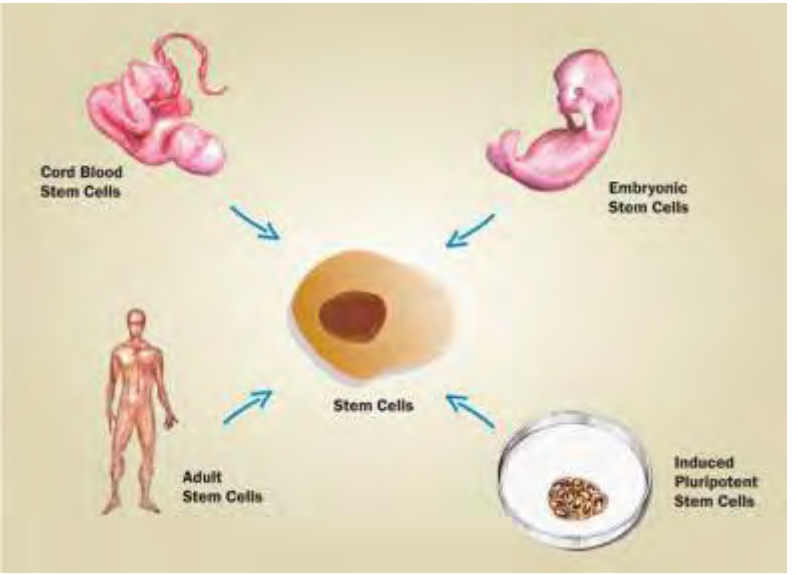
Stem cell therapy has been found to be safe and effective in various conditions such as neurological disorders, orthopedic conditions, diabetes, pulmonary conditions, cardiac conditions, cancer, etc.

What are stem cells?

Stem cells are unspecialized cells in the body with a potential to multiply and differentiate into specialized cells of the body. They have two unique characteristics. Firstly, they have the ability of unlimited self renewal to produce more cells called "daughter cells". Unlike cancer cells, this division of stem cells is highly regulated. Secondly, they can differentiate into specialized cells with specific functions.

Stem cells may replicate through two types of cell divisions: (i) both daughter cells are identical as parent stem cells and continue to contribute to the original stem cell line, (ii) one of two cells is identical to parent stem cells and the second differentiates into more specialized cell lineage. They also secrete paracrine molecules which indirectly help in cytoprotection and repairing the damage via paracrine mechanisms.

Different types of stem cells



Stem cells can be classified depending on their potency or the origin. Based on their potency they are classified as totipotent, pluripotent, multipotent or unipotent. While , based on their origin, stem cells are classified as embryonic stem cells, adult stem cells, umbilical cord blood cells and induced pluripotent stem cells.

1) **Totipotent cells:** Cells with ability to differentiate into cell lineages from all three germ layers: mesoderm, endoderm, and ectoderm including placental cell. They have the capacity to form the whole of the embryo.

2) **Pluripotent stem cells:** Cells with ability to differentiate into cells of all the three germ layers of the embryo, i.e., endoderm, mesoderm and the ectoderm.

3) **Multipotent stem cells:** Cells which give rise to cells of one of the germ cell layers only, either ecto-, meso- or endoderm.

4) **Unipotent stem cells :** Cells which that give rise to cells of one lineage, e.g., hematopoietic stem cells, epidermal stem cells, intestinal epithelium stem cells, neural stem cells, liver stem cells or skeletal muscle stem cells.

Based on their origin, stem cells are also classified as embryonic stem cells, adult stem cells, umbilical cord stem cells and induced pluripotent stem cells.

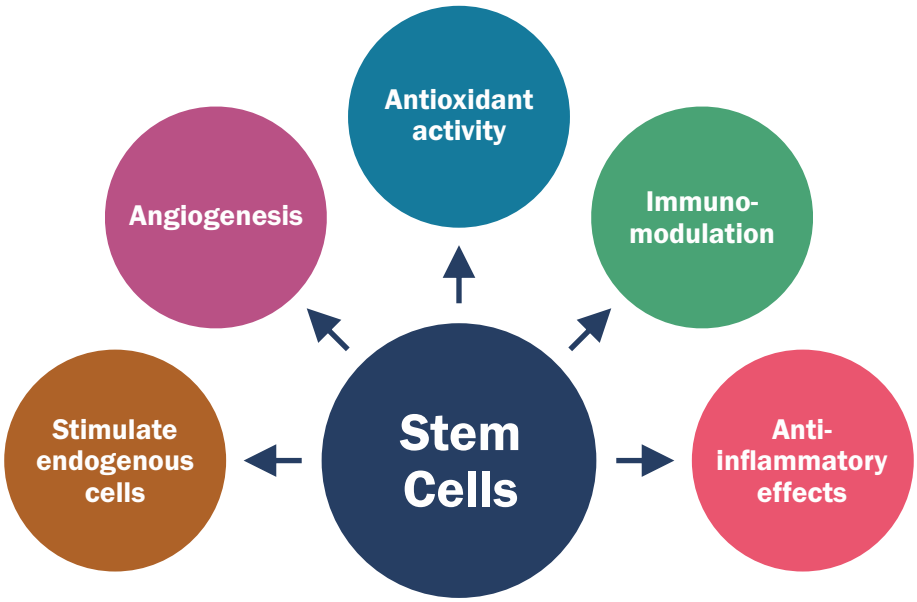
(1) **Embryonic Stem cells:** These are pluripotent cells isolated from the inner cell mass of the blastocyst. They have a potential to replicate indefinitely and differentiate into all germ layers. However, there is a risk of tumorogenicity involved in use of these cells.

(2) **Adult Stem Cells:** Adult stem cells are self-renewing and have ability to differentiate into the mature cell of its resident environment and also, may have transdifferentiating abilities. They are found in liver, brain, bone marrow, adipose tissue, heart, etc. Their quantity and quality decreases with the age. These are a preferred source of stem cells as they do not involve any ethical, moral or legal issues as compared to the use of embryonic stem cells.

(3) **Umbilical Cord Stem Cells:** Umbilical cord blood stem cells can be obtained from the umbilical cord immediately after birth. They are a rich source of hematopoietic and non-hematopoietic stem cells and progenitor cells. Wharton's jelly from the umbilical cord also contains potentially useful stem cells.

(4) Induced Pluripotent Stem Cells: Differentiated somatic stem cells which are reprogrammed to become embryonic like pluripotent stem cells by inducing certain factors.

Mechanism of action in COVID-19



Stem cell therapy is emerging as a new promising treatment for COVID-19 which may attenuate inflammation and also repair and regenerate the lung damage caused by COVID-19. Stem cells exert their immunomodulatory, antioxidant, and regenerative effects which could be beneficial, alone or in combination with other standard treatments in COVID-19.

Much of the critical illness associated with SARS-CoV-2 infection is believed to be the result of a hyperinflammatory response where large amounts of various inflammatory factors such as several cytokines, chemokines and immune reactive cells are produced. Stem cells stimulate endogenous cells and through their immunomodulatory and anti-inflammatory properties help to modulate and thus curb this cytokine storm. They have shown to reduce the expression of pro-inflammatory cytokines.

Mesenchymal stem cells are studied extensively for this purpose. Their safety profile and efficacy is well-established in lung diseases such as ARDS,chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), obstructive bronchiolitis (OB) and bronchopulmonary dysplasia. MSCs have shown to be ACE2- and TMPRSS2-negative, which means the COVID-19 virus cannot attack these cells. In addition, MSCs stimulate endogenous cells to secrete different chemicals and modulate the immune response. They secrete anti-inflammatory molecules like (IL)-10 and growth factors that are required for repair of various tissues like Hepatocyte Growth Factor (HGF), transforming growth factor beta 1 (TGF-β1), Vascular Endothelial Growth Factor (VEGF) etc. This reduces curbs the 'Cytokine Storm' and lung damage. MSCs also have the potential to form new lung tissue or repair damaged lung tissue. MSCs also have an anti-viral effect.

Mesenchymal stem cells when intravenously injected get trapped in the lung, and exert anti-inflammatory, anti-microbial, angiogenic and tissue repair functions within the damaged lung via cell-to-cell contact without engrafting into the tissue. The pulmonary microenvironment could be recovered with the help of these MSCs, thus protecting the alveolar epithelial cells. Hence, pulmonary fibrosis could be prevented, which may lead to recovery of COVID-19.

Clinical use of stem cells

(A) Conventional Indications

Haemopoietic stem cell transplantation is one of the oldest stem cell therapy

which is most widely available. The stem cells are procured from bone marrow, peripheral blood or cord blood. For some applications, the patient's own cells are engrafted. However, allogeneic stem cell transplantation is now a common procedure for the treatment of bone marrow failure and haematological malignancies, such as leukaemia. Donor stem cells are used to reconstitute immune function in such patients following radiation and/or chemotherapy.

(B) Newer indications

Stem cell therapy has immense potential for treating various conditions other than hematopoietic disorders. It may serve as a promising adjunctive therapy where the conventional therapies are inadequate. Cells procured from sources such as bone marrow, umbilical cord blood, adipose tissue, amniotic fluid, and placenta are being explored for non-homologous use. Numerous studies published in India and all over the world have established the therapeutic potential of this treatment in a variety of incurable illnesses such as neurological disorders including autism spectrum disorders, cerebral palsy, intellectual disability,muscular dystrophy, brain stroke, spinal cord injury, motor neuron disease; cardiac and respiratory disorders, wound healing, diabetes, orthopaedic conditions, etc. Ability of stem cells to replace impaired or lost cell types and restore function, is considered to be the major mechanism underlying efficacy of stem cell transplantation. However, other mechanisms, such as the secretion of neurotrophic factors, immune modulation, and stimulation of endogenous neurogenesis also contribute to its therapeutic effects. These cells release desired neurotransmitters, neuroprotective factors, various cytokines and growth factors, and angiogenic factors which may revive or stimulate the regeneration of endogenous neurons and even promote the growth of neurites and synaptogenesis. These cells also have anti-inflammatory and immunoprotective properties. They can promote myelination, improve vascularity, and are known to modify the blood brain barrier.

a. **Autism Spectrum Disorders and Cerebral Palsy:** For these neurodevelopmental disorders there is no standard treatmentand stem cell therapy has shown to be effective. There are 23 scientific publications for autismand 54 scientific publications for cerebral palsy in national and international journals showing safety and efficacy of stem cells. Sharma et al have published world's first study demonstrating the benefits of autologous bone marrow derived cell therapy in autism. Their results showed improvement in speech and communication, behaviour, cognition, attention and concentration alongwith reduced hyperactivity, aggressive

behaviour and repetitive mannerisms. Improvement was also observed in brain metabolism of these patients as seen on PET CT scan. In Cerebral palsy, published results have shown restored limb functions with improved locomotor ability, neck holding, balance and functional independence.

b. **Muscular Dystrophy and Amyotrophic lateral sclerosis:** These neuromuscular disorders do not have any definitive cure. Almost all individuals diagnosed with Duchenne muscular dystrophydie before the age of 25 and most of the patients with Amyotrophic lateral sclerosisdie within the first 5 years of being diagnosed. Stem cell therapy has shown promising outcomes in these conditions. There are 34 scientific publications for muscular dystrophy and 32 for Motor Neuron Disease demonstrating safety and efficacy of stem cell therapy.Results have shown that it helps in halting the progression of the diseasealongwith alleviating symptoms.

c. **Spinal Cord Injury and Traumatic Brain Injury:** Currently, there is no cure available for Neurotraumatic conditions. Majority of patients with severe spinal cord injury remain paraplegic or quadriplegic despite conventional surgery. Patients with traumatic brain injury suffer from neurodeficits. Stem cell therapy has proven to be beneficial in these conditions. There are 93 Scientific publications for spinal cord injury and 15 for traumatic head injury showing safety and benefits of stem cell therapy. Results have shown that it helps in improved limb functions, regaining bowel and bladder control and restoring functional independence. In traumatic brain injury, it helps in improving cognition, memory, speech, fine and gross motor activities, balance and mobility.

d. **Stroke and Dementia:** Neurovascular disorders like brain stroke and dementia do not have any cure. Scientific evidence has shown that stem cell therapy is safe and effective in reversing the neurological damage in these conditions. There are 43 scientific publications for stroke and 10 for dementia. A significant number of patients after stroke despite best medical treatment remain hemiplegic and sometimes aphasic. Stem cell therapy helps in restoring limb function and speech in stroke patients and halts the disease progression in dementia alongwith improving cognition and memory.

e. **Orthopedic conditions:**Stem cell therapy has promising therapeutic potential to treatment of orthopedic conditions such as Osteoarthritis and Avascular necrosis. Bone marrow-derived mesenchymal stem cells (MSCs),

adipose-derived stem cells (ASCs), and synovium-derived stem cells (SDSCs) have demonstrated chondrogenic potential. There are 75 scientific publications proving the safety and efficacy of stem cell therapy. Many of these patients require a complete joint replacement surgery which is a major intervention. Stem cell therapy helps in restoring function specially in older age group people preventing joint replacement.

f. **Limb Ischemia:** There are 117 scientific publications demonstrating safety,feasibility and efficacy ofstem cell therapy in Critical limb ischemia. A significant number of patients with this condition require limb amputation. However, stem cell therapy helps with therapeutic angiogenesis which could significantly promote ulcer healing and reduce the amputation rate.

g. **Ophthalmic conditions:** Current treatments aim at protecting vision and preventing visual impairment by early diagnosis using various methods of intervention such as surgery, ionizing radiation, laser, or drug treatments. Despite the efficiencies of these treatment modalities, they do not provide a complete solution to stop the progression to blindness.Stem cell therapy has the potential to revive degenerated cells or replace cells in ocular disorders and restore vision. There are more than 10 publications demonstrating the safety and efficacy of stem cell therapy in ophthalmic conditions.

Owing to the excellent regenerative and tissue repair capacity of stem cells, they are now being explored for Covid-19 which could cause multi-organ damage and for which no particular therapy is available.

Mechanism of action in Covid 19

Stem cell therapy may attenuate inflammation and also repair and regenerate the lung damage caused by COVID-19. Stem cells exert their immunomodulatory, antioxidant, and regenerative effects which could be beneficial, alone or in combination with other standard treatments in COVID-19.

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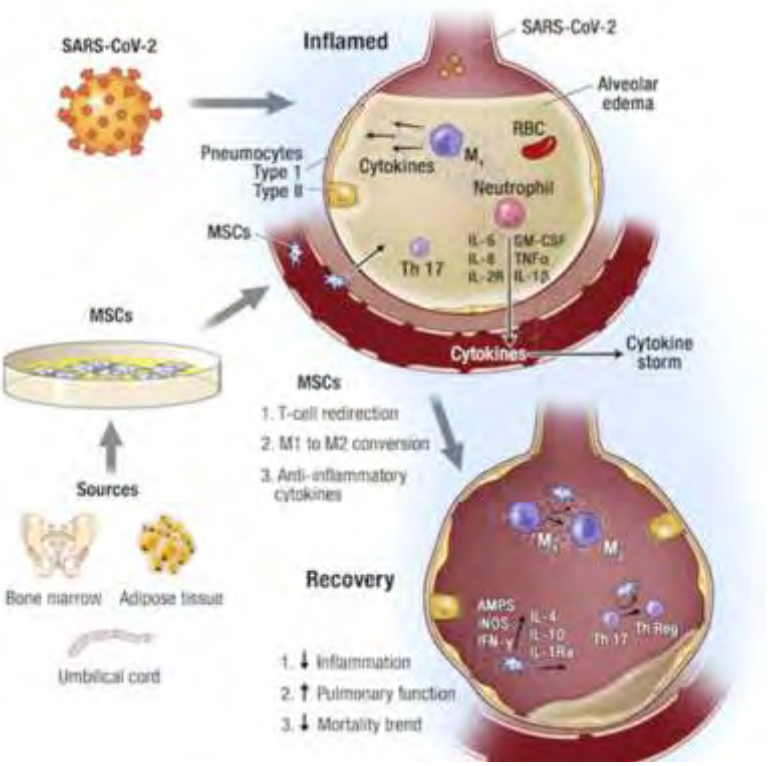

Courtesy : Mayo Clinic

Clinical studies

(A) Published studies

A study in China was published by Leng Z et al. conducted a study on 10 patients with COVID-19 Pneumonia. 7 Patients were intravenously administered with mesenchymal stem cells and were assessed for 14 days, while 3 patients served as controls. It was observed that MSCs were safe, effective and significantly improved the clinical recovery of COVID-19 patients. No adverse events were observed. Significant improvements were noted in pulmonary function and symptoms in all patients within 2 days after MSC transplantation. Among them, two common and one severe patient recovered and were discharged within 10 days.

As compared to the control group, pro-inflammatory TNF-α significantly decreased while the anti-inflammatory IL-10 levels increased in MSC treatment group.

Another study involved a critically ill COVID-19 patient who was on ventilator. The patient was administered with 3 infusions of 5×10^7 human umbilical cord MSC (hUCMSC). Within 4 days of second cell infusion, the patient was able to walk. The essential parameters like T-cell counts were restored back to normal levels. There were no side effects recorded.

(B) Ongoing trials

India: There are 2 ongoing clinical trials studying the effect of stem cells in Covid 19

1. A Phase 1 clinical trial of intravenous administration of mesenchymal stem cells derived from umbilical cord and placenta in patients with novel COVID-19 virus pneumonia

The first clinical trial approved by the DCG(I) registered as CTRI/2020/08/027043 is being conducted at Lokmanya Tilak Municipal General Hospital (LTMGH). It is a Phase 1 study to assess the safety and efficacy of IV administration of mesenchymal stem cells derived from umbilical cord and placenta in patients with COVID-19 viral pneumonia. The trial includes twenty patients aged between 18-65 years with a confirmed diagnosis of COVID-19 on qRT-PCR. The trial is underway with preliminary results showing promising results and no adverse events. Clinical improvement has been

recorded along with improved biochemical blood markers and improved oxygen saturation which indicates the ability of MSCs to prevent the development of cytokine storm with acute respiratory distress syndrome.

2. A Randomized, Controlled, Open Label, Multicentre, Two Arm, Two Dosage, Phase II Study Assessing the Efficacy and Safety of Intravenous Administration of Adult Human Bone Marrow Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells in Patients with Acute Respiratory Distress Syndrome Caused by Pneumonia due to COVID-19

Another registered clinical trial (CTRI/2020/10/028250) is a randomized, controlled, open label, multicentre study to assess the safety and efficacy of IV administration of adult human bone marrow derived, cultured, pooled, allogenic mesenchymal stromal cells in acute respiratory distress syndrome (ARDS) caused by COVID-19, the results of which are awaited.

International : There are around 65 ongoing clinical trials studying the therapeutic potential of stem cells in Covid 19.

NCT Number	Title	Country
NCT04366063	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Iran
NCT04486001	Study of Intravenous Administration of Allogeneic Adipose Stem Cells for COVID-19	United States
NCT04348435	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	United States
NCT04349631	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	United States
NCT04445402	Pediatrics HOT COVID-19 Database in NY Tristate	United States

NCT04392778	Clinical Use of Stem Cells for the Treatment of Covid-19	Turkey
NCT04437823	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	Pakistan
NCT04461925	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs	Ukraine
NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Jordan
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	China
NCT04273646	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	China
NCT04299152	Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19	United States
NCT04565665	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	United States
NCT04447833	Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome	Sweden
NCT04382547	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	Belarus
NCT04371601	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	China
NCT04527224	Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia	United States
NCT04346368	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)	China

NCT04456361	Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19	Mexico
NCT04339660	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	China
NCT04457609	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients	Indonesia
NCT04611256	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19	Mexico
NCT04390152	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	Colombia
NCT04336254	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	China
NCT04362189	Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	United States
NCT04535856	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients	Indonesia
NCT04416139	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19	Mexico
NCT04428801	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	United States
NCT04444271	Mesenchymal Stem Cell Infusion for COVID-19 Infection	Pakistan
NCT04521036	Convalescent Plasma for COVID-19 Patients (CPCP)	Vietnam
NCT04345601	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	United States

NCT04452097	Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS	United States
NCT04331613	Safety and Efficacy of CAStem for Severe COVID-19 Associated With/Without ARDS	China
NCT04333368	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	France
NCT04400032	Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard	Canada
NCT04366323	Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded AdiposeTissue in Patients With Severe Pneumonia Due to COVID-19	Spain
NCT04390139	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19	Spain
NCT04348461	Battle Against COVID-19 Using Mesenchymal Stromal Cells	Spain
NCT04365101	Natural Killer Cell (CYNK-001) Infusions in Adults With COVID-19	United States
NCT04490486	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19	United States
NCT04429763	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia	United States
NCT04537351	The MEseNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19	Australia
NCT04494386	Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS	United States

NCT04397796	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	United States
NCT04445220	A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	United States
NCT04625738	Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome	France
NCT04361942	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)	Spain
NCT04302519	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	
NCT04269525	Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	China
NCT04377334	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	Germany
NCT04467047	Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19	China
NCT04516954	Convalescent Plasma for COVID-19 Patients	Vietnam
NCT04393415	Using PRP and Cord Blood in Treatment of Covid - 19	Egypt
NCT04315987	NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia	Brazil
NCT04522986	An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection	Japan

NCT04629105	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER)	United States
NCT04367077	MultiStem Administration for COVID-19 Induced ARDS (MACoVIA)	United States
NCT04349540	Role of Immune and Inflammatory Response in Recipients of Allogeneic Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19	United Kingdom
NCT04482699	RAPA-501-Allo Off-the-Shelf Therapy of COVID-19	United States
NCT04398303	ACT-20 in Patients With Severe COVID-19 Pneumonia	United States
NCT04371393	MSCs in COVID-19 ARDS	United States
NCT04397471	A Study to Collect Bone Marrow for Process Development and Production of BM-MSC to Treat Severe COVID19 Pneumonitis	United Kingdom

Preliminary results of the clinical trials have shown stem cell therapy to be safe and have presumed efficacy in treating Covid 19. These results indicate that stem cell therapy can be considered as a therapeutic option for treatment of Covid 19.

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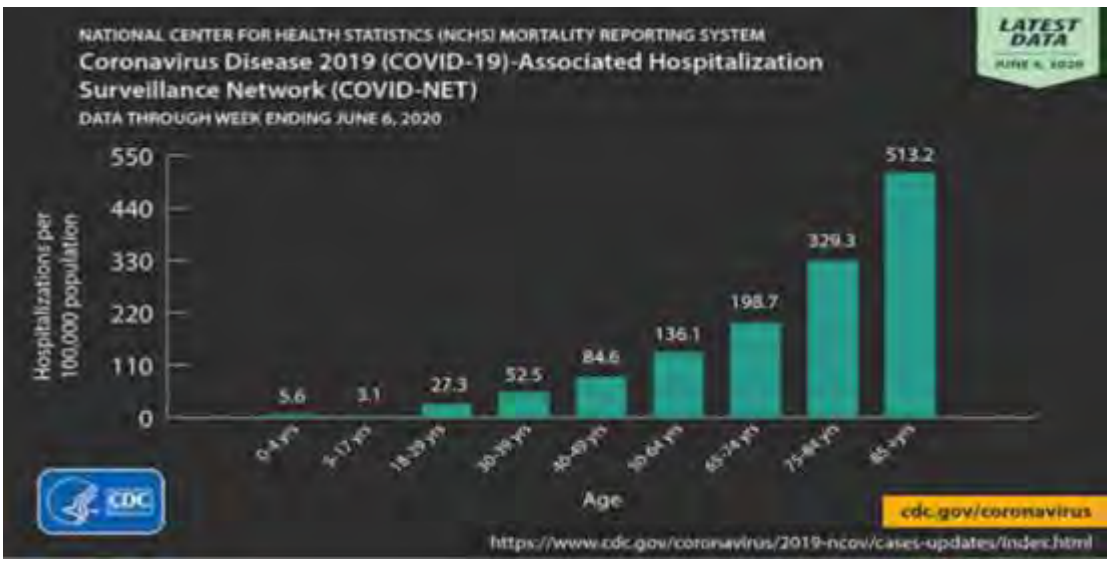
Section G

Biomarkers and Radiological Findings

29 Factors Affecting The Prognosis

1. **Age:** Age is widely reported to be the most important prognostic factor. Advanced age is associated with poor outcome in terms of death, hospitalization, as well as Intensive Care Unit (ICU) admission. A retrospective observation from 113 deaths due to SARS-CoV2 in a cohort of 799 patients admitted in Tongji Hospital in Wuhan, displayed that the median age of deceased patients was 68 years, which was significantly older than the median age of those who recovered (51 years). Death rates were 83% in the age group of ≥ 60 years, 17% in 40-60 years, and 0 in patients < 40 years.

According to the literature patients above 50 years should be regarded as high risk patients.



2. **Sex:** Male gender has been consistently observed as a risk factor for poor outcome in Covid-19.

Amongst the 799 COVID-19 pneumonia patients admitted at Tongji Hospital, Wuhan, male preponderance was observed in the total number of cases, complications, and deaths. Amongst patients who died, M:F ratio was around 7:3 from the 113 deceased.

Similarly, of all the acute respiratory distress syndrome (ARDS) cases 71.4% were male and 28.6% were female (p value >0.05). These findings could be only partially confounded by the higher incidence of comorbidities and smoking habits in males.

Studies have suggested that variations in the severity of Covid symptoms based on age and sex could be due to a protective effect of the female sex hormone estrogen. Females have a more robust immune response to many viral infections. Estradiol and anti-Müllerian hormone (AMH) levels mark high ovarian reserves and are inversely proportional to the severity of disease at any age. The literature has also reported that estrogen can lower the level of ACE2 in the heart, which may modulate the severity of Covid-19 in women. The potential for estrogen treatment in COVID-19, by examining the presence of an association between high estrogen levels and lower levels of COVID-19 infection and severity in women has been studied recently.

3. **Comorbidities:** A meta-analysis of seven studies which included total of 1576 Covid-19 patients showed the most prevalent comorbidities responsible for poor prognosis are hypertension (21.1%), diabetes (9.7%), cardiovascular disease (8.4%) and chronic respiratory disease (1.5%).13

Up to 63% of death occurred in those who had at least one comorbidity amongst the 113 COVID-19 deaths that occurred at Tongji Hospital in Wuhan.1

- Diabetes Mellitus (DM): Diabetes is a common comorbidity along with hypertension, adversely impacting outcomes in COVID-19 subjects. The mortality risk was significantly higher in patients with advanced complicated DM and long duration of disease.

- Obesity: Increased BMI is emerging as a clear cut independent risk factor in COVID-19 patients and underlying insulin resistance may be contributing to higher mortality.

- In a retrospective analysis of age stratified body mass index (BMI) in 3615 COVID-19 patients it was observed that patients with age < 60 years and BMI ≥ 35 kg/m2 were 3.6 times more likely to require ICU than patients with BMI < 25.

- Respiratory comorbidities: Asthma, interstitial lung disease, tuberculosis are the conditions associated with poor lung physiology and underlying comorbidities are considered a high risk group. However no data is available on the proportional mortality rate and rate of infection amongst this group of patients.

4. **Smoking:** Smoking has been a public health problem since decades however there is some controversy regarding its role in COVID-19. Researchers around the globe are studying the effects of nicotine in preventing the Covid-19. Covid-19 enters the host by getting attached to ACE2 receptors. The researchers have proposed that nicotine possibly attaches to the ACE2 receptors, thereby preventing the virus from attaching to them and potentially reducing the amount of virus entering the host body.

A recent study published from Paris's Pitié-Salpêtrière hospital found smokers had a lower chance of developing SARS-CoV2 compared with the general population.24 A trial has been initiated in France to study the effects of nicotine patches in COVID-19 patients.

However, at the same time the hazardous effects of smoking or any kind of tobacco are well known. It causes reduction in lung capacity and increases the risk of respiratory infections; it also can increase the severity of respiratory diseases. COVID-19 being an infectious disease that primarily attacks the lungs, if a smoker gets infected, it can impair lung function making it difficult for the body to fight off coronaviruses and other respiratory diseases. Available literature also suggests that smokers are at higher risk of developing severe COVID-19 outcomes and have higher mortality risk. A review of studies by public health experts convened by WHO on 29 April 2020 found that smokers are more likely to develop severe complications with COVID-19, compared to non-smokers.

Hence, to summarize the relationship between smoking and Covid-19, we could say that the chances of getting infected with Covid-19 might be less in smokers compared to the general population; however, once infected, smokers have severe complications and increased mortality rate due to Covid-19 compared to

non-smokers.

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5. **Cancer-** With regard to different types of cancer, it has been reported that patients with hematological malignancy had the highest risk of poor outcomes, followed by those with lung cancers. Patients with metastatic disease had an even higher risk of death.

6. **Pregnancy:** Pregnant women do not appear more likely to contract the infection than the general population. However pregnancy is a state of partial immune suppression and it alters the normal physiological and immunological responses of the body uniquely. This may increase the risk of complication and severity of disease.

7. **Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers :** Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB) are amongst the most important antihypertensive drugs. However, since the Angiotensin Converting Enzyme (ACE)-2 is primarily involved in the entry of the SARS-CoV2 virus into the host cells, and ACEI and ARB drugs could lead to over expression of this cellular receptor, promoting viral replication, the safety of these drugs was initially questioned.

8. **Blood group-** Various genetic studies have unmasked the possible role of ABO blood groups in determining the outcome of disease.A recent genome association analysis done on 1980 patients with COVID-19 respiratory failure suggested that "A+ve" blood group was associated with higher odds of developing respiratory failure (OR 1.45) whereas blood group "O" had a protective role.(OR 0.65). In this study from Italy and Spain, those with "A+ve" blood group had a 45% higher risk of respiratory failure whilst O blood group had a 35% lower risk.

9. **Blood markers:** Elevated inflammatory markers (C-reactive protein, procalcitonin, ferritin), elevated D-dimer, elevated interleukin-6, neutrophil-to-lymphocyte ratio (N/L ratio).

10. **Ventilatory support:** Need of ventilatory support during the course of hospitalization is said to be an independent predicting factor for poor outcomes and increased mortality rate in Covid-19 patients. Older age with associated comorbidities and need of ventilatory support has shown very high mortality risk. Studies have shown that mortality rates among the patients who require ventilatory support are around 70-80%.

An important problem with mechanical ventilation is the availability of resources. There is some data that suggests the shortage of mechanical ventilators has led physicians to use noninvasive methods to manage seriously ill patients, which may be another factor leading to the high mortality rates. Most of the published data on mechanical ventilation of COVID-19 patients lack transparency regarding resources and clinical decision making, which makes it difficult to interpret the data. Also, mortality may be higher than expected, but excluding all the patients who are still receiving care is causing confusion in correct data analysis and interpretation.

COVID-GRAM, a web-based calculator to estimate the probability that a patient will develop critical illness (defined as intensive care admission, invasive ventilation, or death) has been validated in a study of nearly 1600 patients in China. It relies on the following 10 variables at admission: chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. Additional validation studies, especially outside of China, are required.

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30 Clinical Indicators For Disease Progression

Red flag sign:

According to the literature, if the following signs develop in the Covid-19 patient during the course are likely to deteriorate:

1. Neutrophil Lymphocyte ratio > 3.5
2. P:F ratio less than 300
3. Markedly Raised IL -6 / CRP/ S.Ferritin / D-dimer/LDH/ Triglycerides
4. SpO2 - less than 88% on oxygen.
5. BP < 90/60 mm Hg.
6. Pulse > 120/min or < 55 bpm.
7. RR > 35/ min.
8. ECG major abnormalities.
9. Deteriorating CBC LFT Creatinine
10. Reduced urine output.

Body temperature:

The average body temperature which is generally accepted as normal is 98.6°F (37°C). However, some studies have shown that the "normal" body temperature in adults can have a wide range, from 97°F (36.1°C) to 99°F (37.2°C). Babies and children have a little higher range from 97.9 F to 100.4 F.

Body temperature normally changes throughout the day.

Factors that can determine body temperature are as follows-

- Level of physical activity
- Time of the day (Typically being lowest in the early morning and highest in the late afternoon)
- Age
- Gender
- Eating and drinking status at that time
- The stage in their monthly menstrual cycle, in females

Site of the measurement-

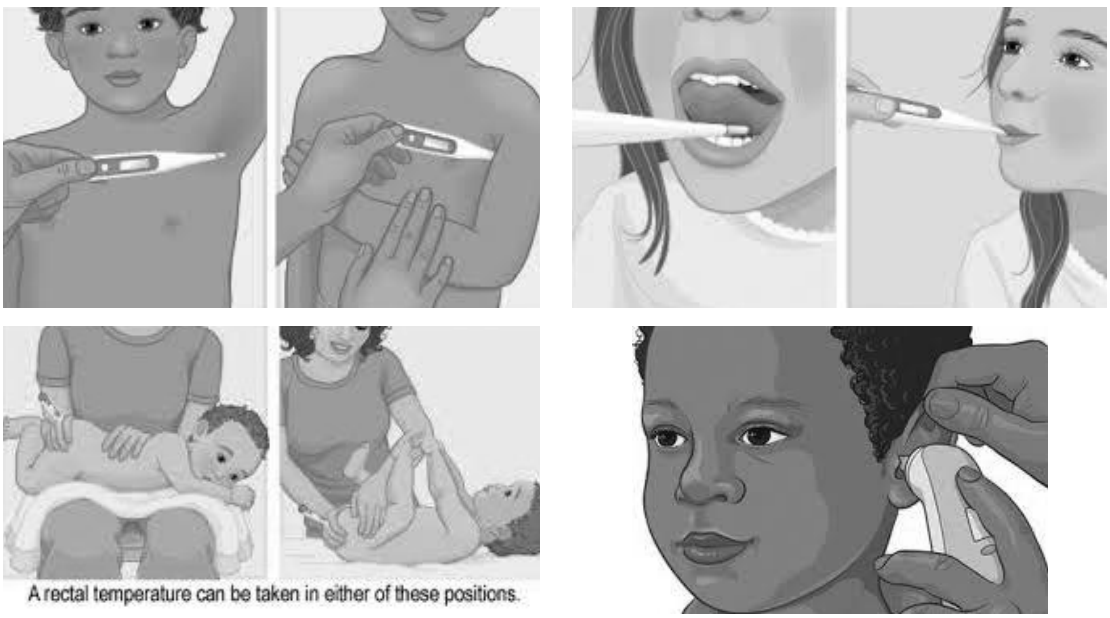

Fig 1, 2, 3, 4 - Site of Measurement

Temperature reading can differ based on the site of measurement you are using. Underarm readings can be a degree lower than the oral reading. Rectal temperature is usually higher by a degree than the oral readings.

Recommended sites to measure temperature based on the age:

Age	Best method
0 to 3 months	Rectal
3 months to 3 years	Rectal, ear, or armpit
4 to 5 years	Oral, rectal, ear, or armpit
5 years to adult	Oral, ear, or armpit

A body temperature which is higher than the normal range is known as a fever. Temperature above 100.4 F is considered a fever in adults.

Classification of the fever based on temperature ranges is as follows:

- Normal temperature 37–38 C 98.6–100.4 F
- Mild/low grade fever 38.1–39 C 100.5–102.2 F
- Moderate grade fever 39.1–40 C 102.2–104.0 F
- High grade fever 40.1–41.1 C 104.1–106.0 F

In children, one can seek medical attention if the child is-

- Under 3 months and the rectal temperature is 100.4 F or more
- 3 months to 3 years and the rectal temperature is more than 102 F
- Older than 3 years and the oral temperature is 103 F or more
- Between 3 and 6 months when the child is having fever with fussiness, irritability or reduced arousal level.

Temperature ranges:

Type of reading	0–2 years	3–10 years	11–65 years	Over 65 years
Oral	95.9–99.5°F (35.5–37.5°C)	95.9–99.5°F (35.5–37.5°C)	97.6–99.6°F (36.4–37.6°C)	96.4–98.5°F (35.8–36.9°C)
Rectal	97.9–100.4°F (36.6–38°C)	97.9–100.4°F (36.6–38°C)	98.6–100.6°F (37.0–38.1°C)	97.1–99.2°F (36.2–37.3°C)
Armpit	94.5–99.1°F (34.7–37.3°C)	96.6–98.0°F (35.9–36.7°C)	95.3–98.4°F (35.2–36.9°C)	96.0–97.4°F (35.6–36.3°C)
Ear	97.5–100.4°F (36.4–38°C)	97.0–100.0°F (36.1–37.8°C)	96.6–99.7°F (35.9–37.6°C)	96.4–99.5°F (35.8–37.5°C)

Why fever happens in covid

Fever is part of the body's own disease-fighting mechanism. A fever begins when your immune system makes more white blood cells to fight any infection. The increase in white blood cells triggers your brain to heat your body up. Fever is the most common symptom of Covid-19 infection. Symptoms usually start to appear 2 to 14 days after you come into contact with the virus.

In an observational study done on 1,420 patients having mild or moderate disease showed that fever was present in 45.4% of the total cases. An analysis of data of a total of 4,203 patients mostly from China reported fever, cough and dyspnoea (80.5%, 58.3% and 23.8%, respectively) as the most common clinical symptoms. According to the literature available, the most commonly reported symptoms in children are fever and cough.

Respiratory rate:

Fig 5 - Respiratory Rate Measurement

A respiratory rate is the number of breaths taken per minute. The normal respiration rate for an adult at rest is 12 to 20 breaths per minute. A respiratory rate under 12 breaths or over 24 breaths per minute at rest is considered abnormal.

Respiratory rates may increase with fever, hypoxia, illness, and other medical conditions. In Covid-19 infected patients, an increased respiratory rate can be seen at the time of admission. Shortness of breath is a common complaint in acute stages of Covid-19 infection, which can be caused due to presence of secretions or pneumonia. It increases the efforts required for breathing, leading to the need of increased number of breaths per minute to meet the baseline oxygen requirement.

Severity number

Severe Covid-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, and blood oxygen saturation of 93% or less.

Pulse rate:

Pulse rate is the number of times heart beats per minute. Pulse rates are slightly different in every person. A normal pulse rate for a healthy adult at rest is considered as 60 to 80 beats per minute. Usually Women have faster pulse rates than men. In children 70 – 100 beats per minute is considered normal.

- Pulse rate can be measured by using the first and second fingertips, one has to press firmly but at the same time gently on the arteries until a pulse is felt(as shown in the figure below).

When the heart is beating more than 100 times per minute, it is known as tachycardia.

Bradycardia is a slower than normal heart rate in which heart beat is less than 60 per minute.

An arrhythmia is a problem with the rate or rhythm of the heartbeat.

SARS-CoV-2 infection is associated with a variety of pro-inflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications.

Yu et al demonstrated that sinus tachycardia was the commonest cardiovascular

SARS-CoV finding with an overall incidence of 72%.

Lau et al additionally described that palpitation, in the form of tachycardia at rest or mild exertion, was noted amongst patients recovering from SARS. Possible causes, according to them, were deconditioning, impaired pulmonary function, impaired cardiac function, cardiac arrhythmia, thyroid dysfunction, anemia, autonomic dysfunction, and anxiety state

It has been reported that in the patients with COVID-19, the most common ECG abnormality is tachycardia; however, it is usually self-limiting, the incidence ranges from 72%; occurence of bradycardia is relatively less common, ranging from 2% to 15%.

Early reports from China suggested an overall cardiac arrhythmia incidence of 17% in patients hospitalized for COVID-19. A higher arrhythmia rate (44%) was observed in patients with COVID-19 admitted to the intensive care unit (ICU).

Oxygen saturation:

Fig 6, 7 - Pulse Oximeter

Oxygen saturation also known as SpO2 is a measure of the amount of oxygen-carrying hemoglobin in the blood relative to the amount of hemoglobin not carrying oxygen

A pulse oximeter (pulse ox) is used to measure the oxygen saturation. It is a noninvasive device which estimates the amount of oxygen present in the blood. Its mechanism works by sending the infrared light into capillaries in the finger, toe, or earlobe. Then it measures how much light is reflected off the gases. A reading indicates what percentage of your blood is saturated, known as the SpO2 level.

A normal reading on pulse oximeters is typically between 95 and 100 percent.

The dark nail polish or cold extremities can cause the pulse ox to read lower than normal.

A below-normal blood oxygen level is called hypoxemia.

Hypoxemia can manifest symptoms like-

- Shortness of breath
- Chest pain
- Confusion and dizziness
- Headache and fatigue
- Tachycardia

One can show symptoms of cyanosis, if oxygen saturation is significantly low. The hallmark sign of this condition is a blue discoloration of your nail beds, skin, and mucus membranes.

A person with COVID-19 who has opted for home isolation should make sure that the SpO2 reading stays consistently at or above 94%. If the number consistently drops below this threshold, timely medical evaluation is warranted.

PaO2- The partial pressure of oxygen, also known as PaO2, is a measurement of oxygen pressure in arterial blood. It reflects how well oxygen is able to move from the lungs to the blood.

FiO2 (the fraction of inspired oxygen)- It is defined as the percentage or concentration of oxygen that a person inhales. The atmospheric air that we inhale on a day to day basis is made up of 21% oxygen, 78% nitrogen and 1% trace elements such as argon, carbon dioxide, neon, helium and methane.

PaO2/FiO2 ratio is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen. at sea level, the normal PaO2/FiO2 ratio is ~ 400-500 mmHg (~55-65 kPa).

Acute respiratory failure requiring mechanical ventilation is a leading cause of mortality in the intensive care unit. Although single peripheral blood oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratios of hypoxemia can effectively risk-stratify patients with acute respiratory distress syndrome.

SpO2/FiO2 ratios have been used frequently over PaO2/FiO2 ratios because they are ubiquitously available and noninvasive.

Silent hypoxia

It has been noted in the patient's of Covid-19 that a person's oxygen levels are so low that they should be fainting, having difficulty in breathing or experiencing organ damage, but instead, they appear physically normal, until eventually, they collapse. This phenomenon is called Happy hypoxia. Therefore, it is very important to closely monitor respiratory rate, signs of hyperventilation,and oxygen saturation in all the suspected cases, even if they are appearing well.

The adequacy of gas exchange is primarily determined by the balance between pulmonary ventilation and capillary blood flow, referred as ventilation/perfusion (V/Q) matching. In the initial phase of COVID-19, several mechanisms contribute to the development of arterial hypoxemia without a concomitant increase in work of breathing. The mechanism of why oxygen levels drop has to do with how well the blood flow through the lungs matches the airflow through the lungs. In certain patients the Covid-19 virus affects both the blood vessels in the lungs, as well as air sacs in the lungs, mismatching the flow of blood and air, causing the oxygen levels to drop.

Dyspnea on walking

Fig 8 - Dyspnea

Shortness of breath (SOB), also known as dyspnea is a feeling of not being able to breathe well enough. The American Thoracic Society defines it as a subjective experience of breathing discomfort that consists of qualitatively distinct

sensations that vary in intensity. Dyspnea is a normal symptom of heavy exertion but becomes pathological if it occurs in unexpected situations[2] or light exertion.

The MRC dyspnoea scale is a questionnaire that consists of five statements about perceived breathlessness: grade 1, "I only get breathless with strenuous exercise"; grade 2, "I get short of breath when hurrying on the level or up a slight hill"; grade 3, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"; grade 4, "I stop for breath after walking 100 yards or after a few minutes on the level"; grade 5, " I am too breathless to leave the house".

In COVID-19, shortness of breath typically sets in between the 4th and 8th day of illness, although it can be as much as 10 days after the onset of symptoms. In post-viral pneumonia increasing fever and productive cough may be symptoms of worsening illness, whereas in COVID-19, worsening dyspnea may be present without any productive cough.

It is important to assess the patient for any sign of dyspnea before discharge which can be done by either subjective method, by asking questions related to difficulty in breathing at rest or on activity, or objectively by asking the patient to perform any activity and then assessing him for any breathing difficulty.

Blood pressure

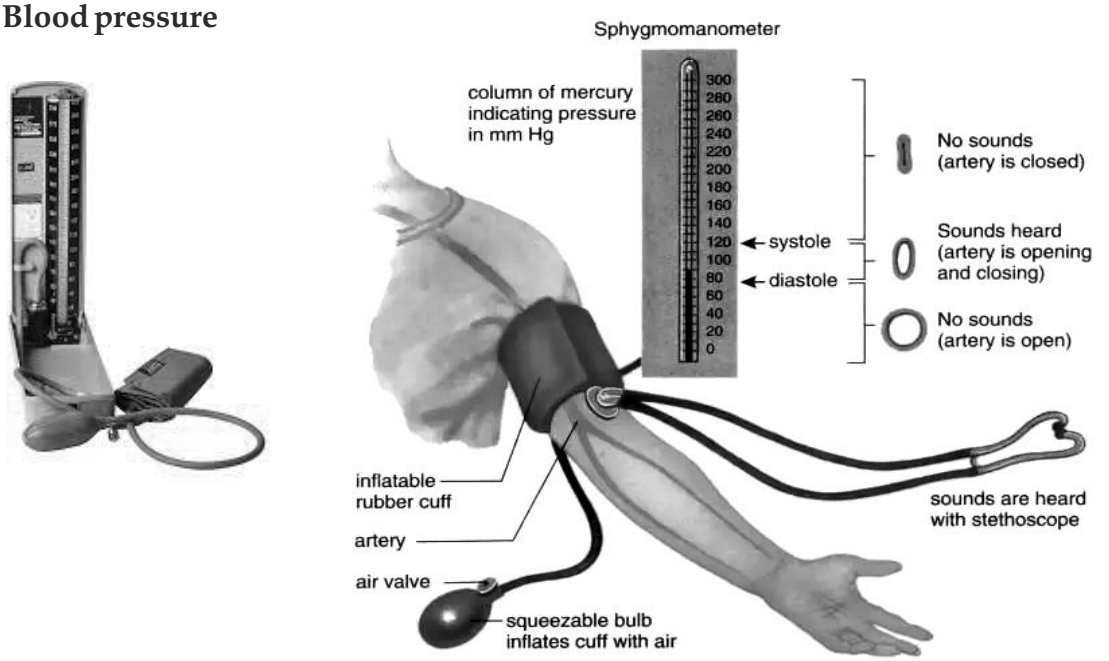

Fig 9, 10 - Blood pressure measurement, sphegmomanometer

It can be defined as the pressure of the blood in the circulatory system. It is often measured for diagnosis since it is closely related to the force and rate of the heartbeat and the diameter and elasticity of the arterial walls. There are two types of blood pressure: Systolic blood pressure refers to the pressure inside your arteries when your heart is pumping; diastolic pressure is the pressure inside your arteries when your heart relaxed in between the beats.

Normal blood pressure is considered to be between 90/60mmHg and 120/80mmHg. High blood pressure is considered to be 140/90mmHg or higher. Low blood pressure is considered to be 90/60mmHg or lower.

The ACE2, a protein facilitates the entrance of SARS-COV-2 into cells and a recent publication found that ACE2 expression was elevated in the lungs of patients with COVID-19 that presented with comorbidities, such as hypertension, when compared with control participants.

The presence of hypertension has been consistently reported as a marker of worse prognosis in patients with COVID-19.

Blood glucose

Fig 11 - Glucose Monitoring

The blood glucose level is the amount of glucose in the blood. Glucose is a sugar that comes from the foods we eat, and it's also formed and stored inside the body. It's the main source of energy for the cells of our body, and it's carried to each cell through the bloodstream.

Blood sugar levels are considered normal when they are less than 100 mg/dL while fasting(8 hours) and less than 140 mg/dL two hours after eating.

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Diabetes is one of the leading causes of morbidity and

mortality throughout the world. The condition is associated with several macrovascular and microvascular complications, that ultimately impact the overall patient's survival. A relationship between diabetes and infection has long been clinically recognized [31]. Infections, particularly influenza and pneumonia, are often common and more serious in older people with type 2 diabetes mellitus (T2DM).

It has been reported that an optimal glycemic control, avoiding acute hyperglycemia, hypoglycemia and glycemic variability may significantly improve the outcome in patients with Covid-19.

Skin rash

Fig 12 - Skin Rash

Angiotensin-converting enzyme 2 (ACE2) is a cellular receptor for COVID-19. Once it enters the host, this peculiar mode of entry of COVID-19 in human cells induces angiotensin II accumulation. Excess angiotensin II may contribute to acute lung injury and vessel dysfunction such as vasoconstriction, vascular permeability and abnormal myocardial remodelling. There is very limited data available on the vascular skin lesions during COVID-19 infection. However, some studies have described the skin symptoms of COVID-19 including erythematous rash, urticaria and chicken pox-like lesions.

The pathophysiology of these lesions is unclear but may include immune dysregulation, vasculitis, vessel thrombosis or neo-angiogenesis. Infected COVID-19 patients with severe respiratory distress have an increased risk of pulmonary embolism suggesting a hypercoagulable state of these patients. Seven patients with acro-ischaemia (toe cyanosis, skin bulla and gangrene) and frequent disseminated intravascular coagulation (4 patients) have been reported during COVID-19 epidemy in Wuhan.

There is a possibility that a patient with COVID-19 might initially present with a skin rash that can be misdiagnosed as another common disease such as dengue.

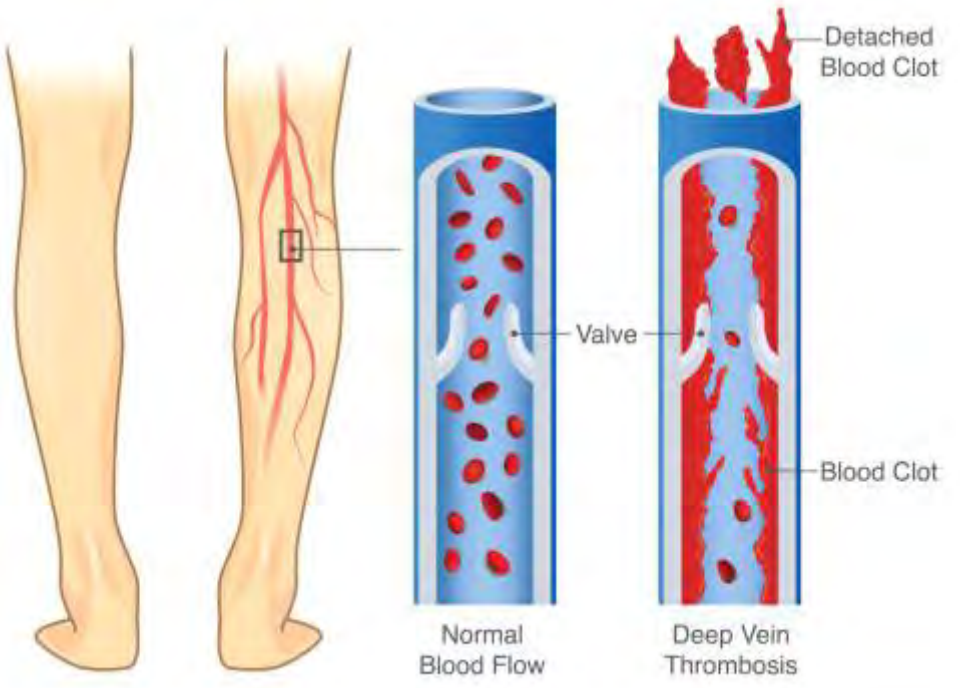

Fig 13, 14, - DVT

The researchers from Russia showed that patients with moderate and severe coronavirus disease (COVID-19) have a high incidence of deep vein thrombosis, indicating that they may necessitate an early administration of anticoagulation therapy as a part of their treatment regimen.

Zhang and colleagues reported on 143 consecutive patients with COVID-19 (mean age, 63; 48% women) who were hospitalized from January 29 to February 29, 2020, at a single academic center and who underwent lower-extremity venous ultrasound scanning. Almost half of the patients (46%) developed a lower-extremity deep venous thrombosis (DVT).

Possible mechanisms for the connection between DVT and COVID-19 may include viral infection–induced release of cytokine, which is also thrombogenic, and the plausible role of angiotensin-converting enzyme receptors in vascular alterations,22 but further study is needed to elucidate the pathophysiology of DVT in COVID-19.

SOFA score (The sequential organ failure assessment score)

The sequential organ failure assessment score (SOFA score), previously known as the sepsis-related organ failure assessment score, is used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. It is useful in predicting the clinical outcomes of critically ill patients.

The Quick SOFA Score (quickSOFA or qSOFA) was introduced by the Sepsis-3 group in February 2016 as a simplified version of the SOFA Score as an initial way to identify patients at high risk for poor outcome with an infection. The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection was associated with a greater risk of death or prolonged intensive care unit stay.

In various studies it has been reported that an older age, number of preexisting comorbidities ≥2, and SOFA score were independent risk factors for death for COVID-19.

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31 Importance of Blood Markers In COVID-19

Although most of the patients with COVID-19 show mild influenza-like symptoms or may be asymptomatic, a small proportion of patients report severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and may also fail to survive. Around 15% of the total Covid-19 patients develop severe complications. The reason why some individuals become critically ill, while others do not, remains unsolved. Comorbidities and laboratory markers can be used to indicate the prognosis. Clinical studies demonstrated that altered levels of some blood markers might be linked with the degree of severity and mortality of patients with COVID-19

Cytokine storm- There is significant literature available which states that in critically ill patients, there are characteristics of hyperinflammation, which consist of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia. These findings suggest a crucial role of a cytokine storm in COVID-19 pathophysiology.

Current clinical practice suggests checking IL-6, D-dimer, lactate dehydrogenase (LDH), and transaminases in addition to routine laboratory tests, in order to identify patients at risk of fatal complications and those who will potentially benefit from anti-IL 6 immunotherapies such as tocilizumab. However, as costly cytokine analysis is not routinely performed in most laboratories, surrogate markers of infection (ferritin, C-reactive protein (CRP)) correlated to IL-6 will be of increasing interest for prognostic value.

1. **CRP (C-reactive protein)-** CRP is a type of protein produced by the liver that serves as an early marker of infection and inflammation. In blood, the

normal concentration of CRP is less than 10 mg/L. In severe cases of Covid19 it has been observed that CRP rises rapidly within 6 to 8 hours and reaches the peak in 48 hours from the disease onset. When the inflammation or tissue damage is resolved, CRP concentration falls, making it a useful marker for monitoring disease severity. A significant increase of CRP was found with levels on average 20 to 50 mg/L in patients with COVID-19. It was also observed that the patients with severe disease had significantly elevated levels of CRP compared to the mild or non-severe patients.

2. **Procalcitonin-** Procalcitonin (PCT) is a widely used biomarker to assess the risk of superimposed bacterial infection and it's progression. PCT helps to discriminate between milder cases and more severe cases. PCT also helps to distinguish between severe bacterial pneumonia and mild viral pneumonia.

   Most COVID-19 patients have very low PCT levels (<0.25µg/L or even <0.1µg/L) at the time of admission, but elevated markers of inflammation such as white blood count (WBC) and C-reactive protein (CRP) indicate that they have inflammation in the lung. However, at a certain point, in the course of the disease, their PCT levels start to increase. This could be due to two reasons. This could possibly happen either because the patient develops secondary bacterial infection or patient starts to deteriorate due to associated covid related pneumonitis.

   Corticosteroids have a good inhibitory effect on inflammatory factors and are often used as an auxiliary treatment for viral pneumonia. However, there has been considerable controversy as to whether COVID-19 patients should be treated with corticosteroids. Russell and colleagues recommend that corticosteroids should not be used in SARS-CoV-2-induced lung injury or shock outside of a clinical trial.25 But a team of front-line physicians from China had a different perspective, they recommended short courses of corticosteroids at low-to-moderate dose, used prudently, for critical patients with COVID-19 pneumonia. An analysis demonstrated that patients treated with corticosteroids had a higher mortality rate. There is a study shows that glucocorticoids inhibit the production of IL-2 and interferon-γ (IFN-γ) in T lymphocytes, shift T cell responses from the Th1 to the Th2 type, induce programmed cell death in a variety of different immunologically relevant cells, including immature T and B cell precursors and mature T cells. That analysis also found that

patients receiving corticosteroid therapy were more likely to develop bacterial infection due to immunosuppression. This could make the disease worse and can increase the chance of mortality.

3. **D-Dimer-** During plasma coagulation, soluble fibrin is generated; D-Dimers are released as characteristic degeneration products of cross-linked fibrin. The increased D-Dimer levels indicate the activation of coagulation and following fibrinolytic processes. The recently published IFCC Guidelines on COVID-19 strongly recommend D-Dimer testing in patients with COVID-19, as the studies on SARS-CoV-2 have shown a high correlation between severity and outcome of COVID-19 in patients with increased D-Dimer levels.

   Marietta et al. reported relatively increased D-Dimer levels as a predictor of developing acute respiratory distress in COVID-19 patients, mentioning the probability of micro pulmonary embolism especially in severe forms of COVID-19.

   An increased risk of venous thromboembolism (VTE) has recently been suggested in intensive care unit (ICU) patients with COVID-19 infection despite adequate thromboprophylaxis. D-dimer is a product of degradation of fibrin acting as a surrogate marker for fibrinolysis and is usually elevated in thrombotic events. The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia and increased D-dimer levels. These hemostatic changes, together with the higher rate of mortality associated with them, indicate some form of coagulopathy that may predispose to thrombotic events, although the cause is uncertain.

4. **Ferritin-** Ferritin is a protein that contains iron and is the primary form of iron stored inside of cells. The small amount of ferritin that is released and circulates in the blood is a reflection of the total amount of iron stored in the body. Ferritin is a key mediator of immune dysregulation. Hyperferritinemia has been shown to be associated with complications in other viral diseases as well such as dengue fever. Various studies have reported that the circulating ferritin concentration could be used to predict COVID-19 progression, and hyperferritinemia is associated with the development of the cytokine storm.

   Active ferritin production during the course of inflammatory diseases can be possible. Macrophages, which produce cytokines and account for the

majority of the immune cells in the lung parenchyma, might be responsible for the secretion of serum ferritin. Moreover, ferritin synthesis can be induced by several inflammatory stimuli including cytokines, such as IL-6

A study concluded that the serum ferritin levels were closely related to the severity of COVID-19 based on an analysis of the peripheral blood of 69 patients with severe COVID-19, which revealed elevated levels of ferritin compared with patients with non-severe disease.

5. **IL-6 (interleukin-6)-** It is one of the main mediators/ cytokine of inflammatory and immune response initiated by infection or injury. Normal range of IL-6 is 5-15 pg/ml. Increased levels of IL-6 are found in more than one half of patients with COVID-19. Levels of IL-6 seem to be associated with inflammatory response, respiratory failure, needing mechanical ventilation and/or intubation and mortality in COVID-19 patients.

   A meta-analysis consisting of nine studies with total of 1426 patients done on IL-6 and its association with outcome in COVID-19, showed that the mean IL-6 levels were more than three times higher in patients with severe or complicated COVID-19 compared to those with uncomplicated disease, and IL-6 levels were also associated with mortality risk.

   Meta-regression also demonstrated that increasing mean IL-6 on admission was associated with an increased likelihood of mortality. That study suggested a cut-off of more than 55 pg/mL for identifying patients at high risk of severe Covid-19.

6. **ESR (Erythrocyte Sedimentation Rate)-** It is a primary indicator of the inflammation. It shows the presence of the infection in the body and the body's fighting mechanism against it. The normal range of ESR should be less than 30mm/hr. As the coronavirus infection causes systemic inflammatory response and immune system dysfunction, it is associated with increased levels of ESR. It was also reported that C-reactive protein has a significant positive effect on ESR.

7. **Lymphocytes-** Lymphocytes are a type of white blood cells, which are primarily responsible for the body's immune response mechanism. Abnormally low counts of lymphocytes, also known as lymphopenia has been observed in the patients with severe Covid-19. The key factor behind the observed lymphopenia is thought to be the inflammatory cytokine

storm.

In an observational study done by Ying Sun et al, data showed the total T lymphocytes, Cd4+, CD8+ T lymphocytes and B lymphocyte counts were all significantly decreased in severe and critically ill patients on admission. These immunological characteristics were also seen in SARS-CoV-1 infection. The study concluded that SARS-CoV-2, has a negative impact on T-cell mediated immunity.

8. **Eosinophil-** Eosinophils are circulating and tissue-resident leukocytes that have potent proinflammatory effects in a number of diseases. They have also been shown to have various other functions, such as immunoregulation and antiviral activity. In an observational study done by Guogang Xie et al,, reports showed significantly reduced peripheral blood eosinophils (EOS) among most patients regardless of the severity of the diseases at the early stage, which had not been reported in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) or the other types of pneumonia.

9. **N/L ratio-** Neutrophil-to-lymphocyte ratio (NLR) is a simple parameter to assess the inflammatory status of a subject. It has proven its usefulness in the stratification of mortality in major cardiac events, as a strong prognostic factor in several types of cancers, or as a predictor and a marker of inflammatory or infectious pathologies and postoperative complications. The study has identified that normal NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.13.

   The NLR was reported as the most useful prognostic factor affecting the prognosis for severe illness patients with Coid-19 pneumonia. According to that study it was recommended that in the patients with age less than 50 years old and NLR < 3.13 who are at very low risk should be treated in a community hospital or home isolation. Patients with age more than 50 years old and NLR ≥ 3.13 who are low risk need to be general isolation ward. Patients with age more than 50 years and NLR < 3.13 are at moderate risk, and should be admitted to isolation ward with respiratory monitoring and supportive care. Patients with age more than 50 years and NLR ≥ 3.13 are at high risk and should be transferred to ICU with invasive respiratory support equipment.

10. **AST (aspartate aminotransferase) and ALT (alanine aminotransferase) levels-** These enzymes are predominantly present in the liver cells and to a some extent in the muscle cells. In the cases of liver injury or damage, the liver cells spill these enzymes into the blood, raising the AST and ALT enzyme blood levels. Recently, scientists have been studying the impact of COVID-19 on other organs, as a number of reports have indicated that more than half of patients with severe COVID-19 showed varying levels of liver disease. One study has postulated that the SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, leading to cholangiocyte dysfunction and inducing a systemic inflammatory response leading to liver injury. A study reported that compared to patients with normal liver tests at admission, those who had abnormal liver test results in form of elevated ALT and AST levels, especially had significantly higher risks of developing severe pneumonia; it also reported that the liver test abnormalities can be used as a predictor for the severity of the disease.

11. **Direct Bilirubin-** Bilirubin is a breakdown product of hemoglobin. Unconjugated bilirubin is transported to the liver, where it is conjugated and excreted via the bile ducts. Total Bilirubin describes the sum of unconjugated and conjugated bilirubin. Elevated total bilirubin levels can indicate different types of liver damage or an increased hemolysis rate. Normal bilirubin level is less than 0.3 mg/dL (less than 5.1 μmol/L) for conjugated bilirubin, and 0.1 to 1.2 mg/dL (1.71 to 20.5 μmol/L)for total bilirubin.

    Several systematic reviews of existing studies state elevated total bilirubin as one of the abnormal diagnostic markers in COVID-19 patients. Further, several meta-analyses found increased total bilirubin levels to be linked with an unfavorable progression of COVID-19. In five studies, patients with severe Covid-19 displayed higher bilirubin levels compared to those with milder forms.

12. **Serum albumin-** Albumin is an essential binding and transport protein for various substances in plasma and maintains the osmotic pressure of blood. Decreased serum concentrations of albumin can be caused by liver damage, during the acute phase inflammatory processes, or by increased excretion in the kidney. The recently published IFFC Guide on COVID-19 suggests testing for albumin in patients with COVID-19. Low levels of serum albumin are reported in patients with severe forms of the disease

and hypoalbuminemia was associated with mortality in hospitalized patients.

13. **Creatinine level-** In a healthy individual, plasma concentration of creatinine is quite constant. Therefore increasing plasma creatinine values can indicate decreased excretion i.e. impaired kidney function. The IFFC Guide on COVID-19 strongly suggests monitoring creatinine in patients with COVID-19 for early identification of kidney injury; because, a study done on 701 patients reported increased serum creatinine and reduced GFR in 14.4% and 13.1% respectively. Also, kidney disease is also associated with increased mortality in Covid-19.

14. **LDH:** Lactate dehydrogenase (LD or LDH) is an intracellular enzyme found in cells in almost all organ systems, which is involved in energy production. It can be used as a general indicator of the existence and severity of acute or chronic tissue damage in the body. LDH levels have been associated with poor outcomes in patients with other viral infections in the past as well. Severe infections may cause cytokine-mediated tissue damage and associated release of LDH. Since LDH is present in lung tissue, greater amounts of LDH can be possibly released in the circulation in the patients of Covid-19, as Covid-19 is characterized by interstitial pneumonia, and acute respiratory distress syndrome.

    In an analysis, elevated LDH values were associated with 6-fold increased odds of severe COVID-19 disease and a >16-fold increase in odds of mortality. Therefore, it was recommended that the patient's LDH should be closely monitored for any of signs of disease progression or decompensation.

15. **ABG-** An arterial blood gas (ABG) analysis measures oxygen and carbon dioxide levels in the blood. It also measures the body's acid-base (pH) level. The normal values for parameters are pH of 7.35-7.45, PaO2 75-100 mmHg, and PaCO2 35-45 mmHg.

    Arterial blood gases yield a more precise measure of gas exchange. With knowledge of PaO2 , PaCO2 , and FIO2 , the alveolar-to-arterial oxygen gradient can be rapidly calculated. The alveolar-to-arterial oxygen gradient enables more precise evaluation of the pathophysiological basis of hypoxemia. hypoxemia with COVID-19 is usually accompanied by an increased alveolar-to-arterial oxygen gradient, signifying either ventilation–perfusion mismatch or intrapulmonary shunting.

The dominant respiratory feature of coronavirus disease (COVID-19) is arterial hypoxemia greatly exceeding abnormalities in pulmonary mechanics (decreased compliance). Many patients are intubated and placed on mechanical ventilation early in their course. ABG analysis plays an important role in the clinical decision making about need of mechanical ventilation support for a Covid-19 patient.

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32 Radiological Findings of COVID-19

The recent literature about radiological findings in coronavirus disease 2019 (COVID-19) is primarily focused on findings of CT scan more than chest X-ray, because CT scan is more sensitive than chest radiography.

The primary findings of COVID-19 on chest radiograph and CT are those of atypical pneumonia or organizing pneumonia. But imaging studies have limited sensitivity for COVID-19, as in mild or initial courses of disease approximately 18% chest radiographs or CT demonstrated normal findings. This was reduced to 3% in severe disease.

Chest radiograph-

Even if it is less sensitive than the chest CT scan, chest radiography is typically the first-line imaging modality used for patients with suspected COVID-19. Use of portable radiography units is preferred to avoid the risk of contamination. More reliable findings can be seen about 10-12 days after the onset of the symptoms.

The most frequent findings are airspace opacities, which can be described as consolidation. Ground glass opacities (GGO). The distribution is most often bilateral, peripheral, and lower zone predominant 89.97. In contrast to parenchymal abnormalities, pleural effusion is rare (3%).

Pulmonary Infiltrates

Airspace opacities -

Air space opacification can be described as filling of the pulmonary tree with

material that attenuates x-rays more than the surrounding lung parenchyma. It is one of the many patterns of lung opacification and is equivalent to the pathological diagnosis of pulmonary consolidation.

In radiological studies, it presents as increased attenuation of the lung parenchyma causing obscuration of pulmonary vessels, without significant loss of volume, in the segment(s) affected.

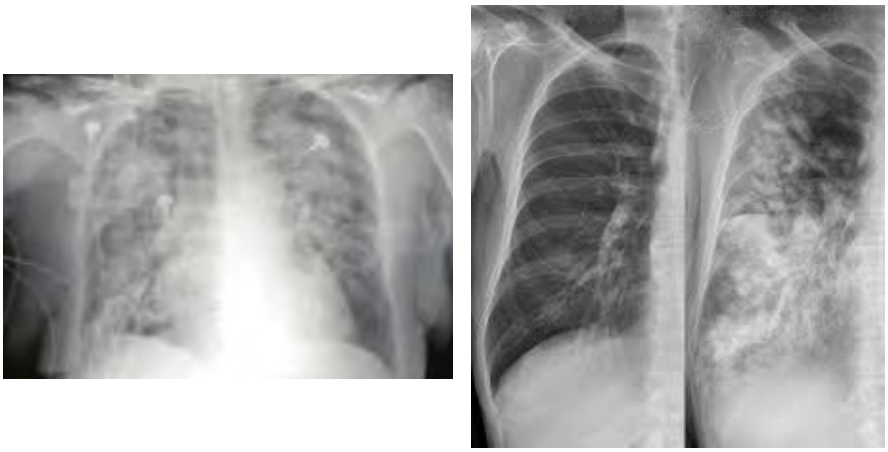

Fig 1, 2 - Air Opacity

Consolidation-

Fig 3, 4 - Cansolidation

Consolidation is the result of replacement of air in the alveoli by transudate, pus, blood, cells or other substances. Consolidation occurs through accumulation of inflammatory cellular exudate in the alveoli and adjoining ducts. The most common cause of consolidation is pneumonia. It can be seen as an ill-defined homogeneous opacity obscuring vessels.

Pleural effusion-

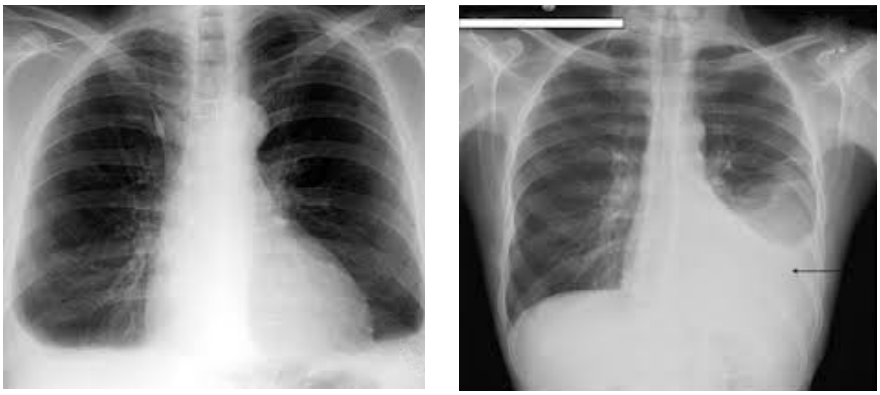

Fig 5, 6 - Plural Effusion

It can be seen in later stages of Covid-19, but is relatively rare (2% of all the cases). A pleural effusion can be described as a buildup of fluid in the pleural space, i.e. an area between the layers of tissue that line the lungs and the chest wall.

Radiograph scoring-

To quantify the extent of infection, a severity score can be calculated by the Radiographic Assessment of Lung Edema score proposed by Warren et al.

A score of 0–4 is assigned to each lung depending on the extent of involvement by consolidation or ground glass opacities

0 - no involvement
1 - 25% involvement
2 - 25%–50% involvement
3 - 50%–75% involvement
4 - 75% involvement

The final severity score can be calculated by adding the scores for each lobe of the lung.

CT scan finding

Initial CT scan findings in COVID-19 cases include bilateral, multilobar ground glass opacification (GGO) distributed peripherally or posteriorly, mainly in the lower lobes and occasionally in the middle lobe. Superimposed Consolidation as the initial imaging presentation mainly in the elderly population. Some of the

less common findings include septal thickening, bronchiectasis, pleural thickening, and subpleural involvement and they mainly present in the later stages of Covid-19.

With the disease progression some of the uncommon signs can also be seen including pleural effusion, pericardial effusion, lymphadenopathy, cavitation, bronchiectasis, nodules, CT halo sign, and pneumothorax.

CT-pattern of COVID-19 and other viral pneumonias has a significant overlapping pattern.

A Chinese retrospective study conducted on 21 patients with COVID-19 reported that on chest CT 71% of cases presented bilateral involvement, 57% ground-glass opacities, 33% rounded opacities, 33% peripheral distribution, 29% consolidation with ground-glass opacities and only 19% of the patients presented crazy-paving pattern.

Ground glass opacities

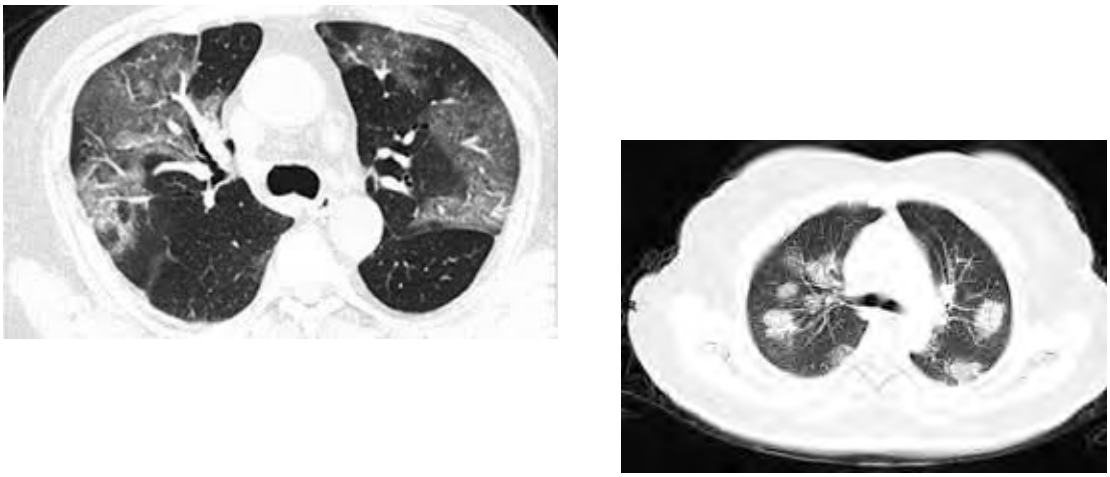

Fig 7, 8 - Ground Glass Opacities

It can be described as an area of increased attenuation in the lung on computed tomography (CT) with preserved bronchial and vascular markings. The most common finding in COVID-19 infections is ground glass (GGO) pattern is. Usually it presents as a multifocal, bilateral and peripheral, but in the early phase of the disease the GGO may present as a unifocal lesion, most commonly located in the inferior lobe of the right lung.

Crazy paving

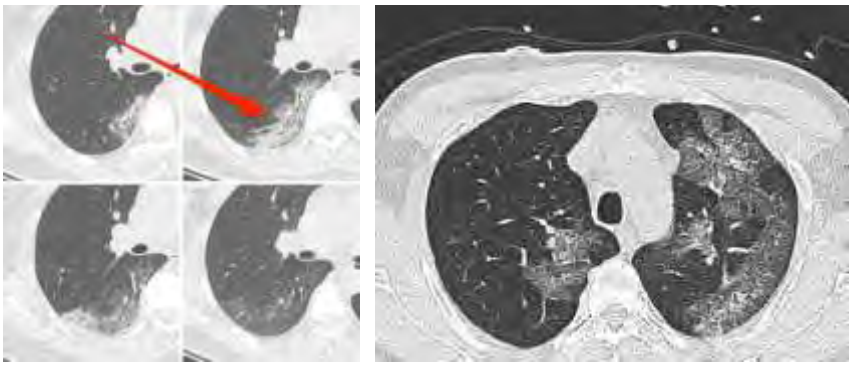

Fig 9,10 - Crazy Paving

It is usually seen in the later stages of the disease.

Crazy paving can be described as the appearance of ground-glass opacity with superimposed interlobular septal thickening and intralobular septal thickening, seen on chest HRCT. It is a nonspecific finding that can be seen in a number of conditions.

Vascular dilatation

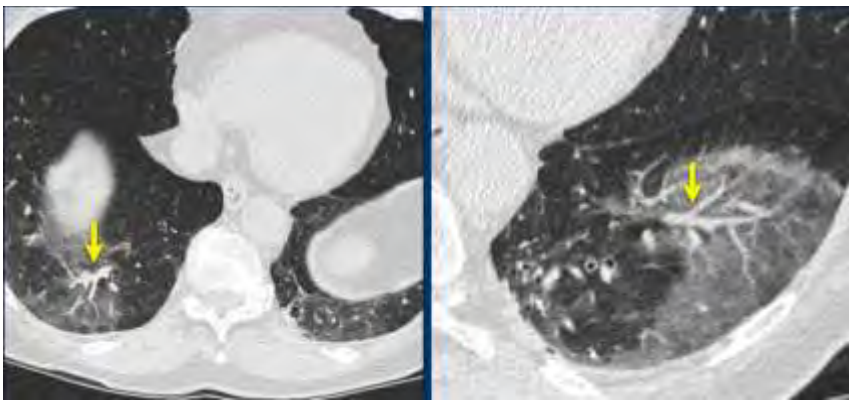

Fig 11 - Vascular Dilatation

The widening of the vessels (arrow) in the area of ground glass is also commonly seen.

Medium to small vessel dilatation is highly prevalent in COVID-19 pneumonia, and it is not confined to areas of diseased lung, and often involves subpleural vessels, suggesting a diffuse vascular process.

The pulmonary response to pneumonia is generally characterized by hypoxic pulmonary vasoconstriction and reduced perfusion to the sites of parenchymal disease, resulting in shunting of blood away from most affected and toward less affected regions – a beneficial matching of ventilation and perfusion. The findings of frequent and pronounced dilation of vasculature to regions of diseased lung may be suggestive of disordered vasoregulation, leading to significant ventilation and perfusion mismatch even early in the disease.

Traction Bronchiectasis

Another usual finding is traction bronchiectasis in the areas of ground glass.

Traction bronchiectasis can be explained as a distortion of the airways secondary to mechanical traction on the bronchi from fibrosis of the surrounding lung parenchyma. Bronchiectasis can be found at the later stage, often accompanied by marginal contraction, suggesting that the lesion is at the repair stage caused by fiber traction.

An air bronchogram is a tubular outline of an airway made visible by filling of the surrounding alveoli by fluid or inflammatory exudates. Air bronchogram is not specific to COVID-19, but it helps distinguish the virus from other bacterial pneumonia. Bronchiectasis is also very common and not specific to COVID-19, but it helps indicate the progress of the disease.

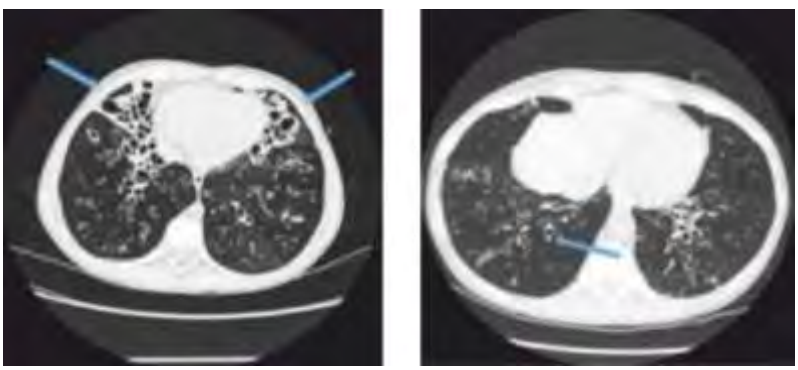

Fig 12 - Bronchiectesis

Subpleural bands and Architectural distortion

In some cases there is architectural distortion with the formation of subpleural bands.

In architectural distortion the normal pulmonary bronchial, vascular, fissural or

septal anatomy is disrupted and manifested as loss of smooth course of the fissures, crowding of dilated bronchioles or vessels with angulated course.

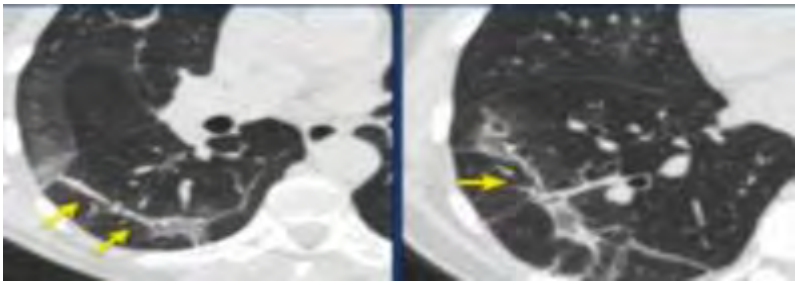

Fig 13 - Architechral Distoration

CT severity score (CTSS)

This score uses lung opacification as a substitute for an extension of the disease in the lungs. According to the anatomical structure, the 18 segments of both lungs are divided into 20 regions, in which the posterior apical segment of the left upper lobe is subdivided into apical and posterior segmental regions, while the anteromedial basal segment of the left lower lobe is subdivided into anterior and basal segmental regions.

The lung opacities in all of the 20 lung regions are subjectively evaluated on chest CT using a system attributing scores of 0, 1, and 2 if parenchymal opacification involved 0%, less than 50%, or equal or more than 50% of each region respectively. The CT-SS is calculated by doing the sum of the individual scores in the 20 lung segments, which will be ranging from 0 to 40 points.

Severity score

Another method to score the severity is by scoring the percentages of each of the five lobes that are involved:

1- < 5% involvement
2- 5%-25% involvement
3- 26%-49% involvement
4- 50%-75% involvement
5- > 75% involvement.

The total CT severity score is calculated by adding the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all

the five lobes show more than 75% involvement.

CORADS:

The level of suspicion of COVID-19 infection is graded from very low or CO-RADS 1 up to very high or CO-RADS 5 based on the HRCT findings. Also, the severity and stage of the disease can be determined with the remarks on comorbidity and a differential diagnosis.

CORADS 1

COVID-19 is highly unlikely.

The CT scan shows normal findings or the findings indicate a non-infectious disease like congestive heart failure, sarcoid, histoplasmosis, malignancy, UIP or fibrotic NSIP

Clinicians should take note that it can show normal findings for the first few days of a mild infection when the CT scan is done.

This was modeled on LI-RADS, in which cases that have no nodules or that have nodules with definitely benign features are reported together, as opposed to BI-RADS, in which category 1 refers to normal findings only, we consider this approach more suitable for patients with potential COVID-19; concomitant findings are frequent in the lung, and there is considerable interobserver variability regarding which findings are normal. According to our definition, mild or severe emphysema, perifissural nodules, lung tumors, and fibrosis are classified as CO-RADS category 1 findings. This category is identical to the "negative for pneumonia" category of the RSNA consensus statement.

CORADS 2

Level of suspicion of COVID-19 infection is low.

Findings consistent with other infections like typical bronchiolitis with tree-in-bud and thickened bronchial walls, tbc.

No typical signs of COVID-19.

The CT-image can show findings of bronchiectasis, bronchial wall thickening and tree-in-bud.

There are no ground glass opacities.

CO-RADS category 2 implies a low level of suspicion for pulmonary involvement by COVID-19 based on CT findings in the lungs typical of infectious origin that are considered not compatible with COVID-19. Examples are bronchitis, infectious bronchiolitis, bronchopneumonia, lobar pneumonia, and pulmonary abscess. Features include tree-in-bud sign, a centrilobular nodular pattern, lobar or segmental consolidation, and lung cavitation. These features are similar to the ones in the "atypical appearance" category of the RSNA consensus statement. Cases with smooth interlobular septal thickening with pleural effusion, which is also part of this RSNA category, are assigned to CO-RADS category 1 if considered typical for interstitial pulmonary edema or are assigned to CO-RADS category 3 if ground-glass opacities that may mimic pulmonary involvement by COVID-19 are also present. This choice was made because CO-RADS describes the pulmonary, not cardiac, involvement of COVID-19.

CORADS 3

COVID-19 unsure or indeterminate.

CT abnormalities indicate infection, but unsure whether COVID-19 is involved, like widespread bronchopneumonia, lobar pneumonia, septic emboli with ground glass opacities.

CO-RADS category 3 implies equivocal findings for pulmonary involvement of COVID-19 based on CT features that can also be found in other viral pneumonias or noninfectious causes. Findings include perihilar ground-glass opacity, homogenous extensive ground-glass opacity with or without sparing of some secondary pulmonary lobules, or ground-glass opacity together with smooth interlobular septal thickening with or without pleural effusion in the absence of other typical CT findings. CO-RADS category 3 also includes small ground-glass opacities that are not centrilobular (otherwise they would be CO-RADS category 2) or not located close to the visceral pleura (otherwise they would be CO-RADS category 4). In addition, it contains patterns of consolidation compatible with organizing pneumonia without other typical findings of COVID-19. This category partially overlaps with the indeterminate appearance category of the RSNA consensus statement but includes those cases with lower likelihood for COVID-19.

CORADS 4

In CO-RADS 4 the level of suspicion for Covid-19 is high.

There can be a suspicious findings which are not extremely typical:

- Unilateral ground glass
- Multifocal consolidations without any other typical finding
- Findings suspicious of COVID-19 in underlying pulmonary disease.

CO-RADS category 4 implies a high level of suspicion for pulmonary involvement by COVID-19 based on CT findings that are typical for COVID-19 but also show some overlap with other (viral) pneumonias. Findings are similar to those for CO-RADS category 5; however, they are not in contact with the visceral pleura, nor are they located strictly unilaterally in a predominant peribronchovascular distribution or superimposed on severe diffuse preexisting pulmonary abnormalities. CO-RADS category 4 consists of the features of the indeterminate appearance category of the RSNA consensus statement that are associated with a higher likelihood of COVID-19.

CORADS 5

Highly suspicious of Covid-19.

CO-RADS category 5 implies a very high level of suspicion for pulmonary involvement by COVID-19 based on typical CT findings. Mandatory features are ground-glass opacities with or without consolidations in lung regions close to visceral pleural surfaces, including the fissures, and a multifocal bilateral distribution. Other classifications only describe a peripheral location, but we found that the vicinity to the minor or major fissure is also typical. Subpleural sparing can be present. We found that the previously described lower lobe predominance is frequently not present in otherwise typical RT-PCR–positive cases; therefore, lower lobe predominance was excluded as a required feature.

CO-RADS category 5 requires the presence of at least one confirmatory pattern that aligns with the temporal evolution of the disease. The pattern that has been described early in the course of COVID-19 is dominated by multiple ground-glass areas, which often show (half) rounded and unsharp demarcation but can be accompanied by sharply delineated ground-glass areas that outline the shape of multiple adjacent secondary pulmonary lobules. The crazy paving pattern, which has been described as appearing later in the course of the disease, shows visible intralobular lines. As the disease progresses, more consolidations occur within the areas of ground-glass opacity. Finally, opacities that resemble organizing pneumonia occur, such as reverse halo signs or ground-glass opacity with extensive subpleural consolidations and air bronchograms.

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Section H

Preventive Measures at Healthcare Set Up

33 Family Physician Clinic Set Up

A general practitioner (GP) is a doctor who treats acute as well as chronic illnesses and provides preventive care, health education and treatment to the patients.

The types of illness that present in an undifferentiated way at an early stage of development, which may require urgent intervention can be managed by the general practitioner. In the ongoing Covid-19 pandemic, not only the patient burden increased on the Family Physician but also the risk of contracting infection from any of the patients visiting the clinic. Family Physician has to be very attentive and careful to prevent the spread of the virus amongst his patients as well as staff members. Hence monitoring of the symptoms, taking basic infection prevention and control measures and providing efficient health care services all at the same time is the prime responsibility of the Family Physician.

In the ongoing pandemic it is the Family Physician's responsibility to learn about the health issues which may have increased or have gone unnoticed during the lockdown period including mental health issues. Family Physician can support the patient's decision of self-care and self-management at home with adequate online guidance as well as can help with referrals if needed.

In this chapter, we are trying to focus on the key areas to be considered in a Family Physician set up to prevent the spread of the virusProvide detailed information about coronavirus disease 2019 (COVID-19), and why it is important to contain the outbreak to all the staff members.

- Provide proper training and guidance about how to prevent transmission of the disease.

- Keep the admin and nursing staff informed on how to advise patients about changes in office procedures (e.g., calling prior to arrival if the patient has any signs of a respiratory infection and taking appropriate preventive actions) and developing plans for management if they are exposed to COVID-19.
- Educate the security, admin, nursing as well as sanitation worker members about proper infection control procedures, including handwashing, good respiratory hygiene and proper use of personal protective equipment, including masks, gowns and gloves.
- Train the nursing and admin staff about taking temperature, blood pressure with minimally touching the patient to prevent the spread.
- Information about the symptoms and clinical course of the Covid-19 should be provided to the nursing staff and reception team.

- Office Preparedness
- Examination area:
  - Facility should have a ready schedule and planning list of daily patient flow, triage, and treatment.
  - Install compartments or dividers to reduce or eliminate exposures by shielding staff and other patients from possibly infected individuals.
  - The workplace should be well ventilated and avoid working in an airconditioned room.
  - Install hand sanitizer disposers, face shields/goggles, medical masks, gloves, and gowns for all caregivers and staff to use when within six feet of patients with suspected COVID-19 infection.
  - Medical masks should be worn at all times while in the clinic.
  - After delivering care, exit the room as quickly and directly as possible (i.e., complete documentation in the clean area).
  - Ensure adherence to standard precautions, including airborne precautions and use of eye protection. Educate about proper donning and doffing methods of personal protective equipment(PPE). Make sure that the separate doffing area is available which is appropriately maintained and medical infectious waste containers are available and also are not over-filled. All other equipment necessary for doffing should also be available

and in good working order.

- Following guidelines for different settings should be followed to wear PPE :

  1. Help/registration desk, doctors chamber, pharmacy counter, sanitary staff- Triple layer medical mask, latex examination gloves.

  2. Dental, ENT, ophthalmologist chambers- N-95 mask, goggles, latex examination gloves, and face shield.

- Staff who have increased risk of covid-19 exposure should be identified and prophylactic management should be done.
- Prepare appropriate office and medical equipment cleaning routines. Staff members can be assigned the schedules in such a way that high-touch surfaces get cleaned every 1-2 hourly to avoid the infection. Managing the laundry, food service utensils, and medical waste should also be performed in accordance with routine procedures.
- Educate staff about appropriate waste disposal using colour coding for different types of waste.
- For example,
- Red – anatomical (e.g. blood,synges, needles)
- Orange – clinical/infectious
- Yellow – clinical/highly infectious.
- Black- municipal waste – ie. not clinical or medical waste

Patient waiting area:

- Install hand sanitizer dispensers and hand washing steps guide in form of posters in the waiting lobby.
- Limit the number of visitors accompanying patients.
- Limit the number of people in the elevators.
- Schedule the appointments in such a way that the waiting time will be minimal and social distancing will be maintained in the waiting room, you can also ask the patients to wait outside or in their vehicles until their turn comes

Triage area

- Develop a triage protocol for your practice based on patient and community outbreak.
- Recommend that patients with respiratory symptoms and fever call the office before arrival.
- Waiting room seating should be rearranged to maintain at least 6 feet distance.
- Consider arranging a separate entrance for symptomatic patients.
- Provide no-touch waste containers with disposable liners in all reception, waiting, patient care, and restroom areas.
- Provide alcohol-based hand rub and masks in all reception, waiting, patient care, and restroom areas for patients with respiratory symptoms. Always keep soap dispensers stocked with handwashing signs.
- Discontinue the use of toys, magazines, and other shared items in waiting areas, as well as office items shared among patients, such as pens, clipboards, phones, etc.
- Use dedicated equipment, including stethoscopes and thermometers, in the triage area. This equipment should be cleaned with appropriate cleaning solutions for each patient.
- Daily screening should be done when the patient arrives using an infrared thermometer to avoid contamination and pulse oximeters. Make sure the pulse oximeter is cleaned after every single patient use.

Cleaning

- Increase the frequency of cleaning and sanitization in the facility. Use alcohol based sanitizers (with at least 60%-70% alcohol) and diluted bleach solutions for cleaning.
- Bleach solution can be prepared by mixing 5 tablespoons of 5.25–8.25% bleach per gallon of water or 4 teaspoons of 5.25–8.25% bleach per quart of water. Water in use should be at the room temperature.
- Bleach solutions will be effective for disinfection up to 24 hours.
- Frequently clean the high-touch areas like door handles, elevator buttons and switches, telephones with 1% Sodium Hypochlorite Solution.
- Keep adequate spacing between two appointments to allow cleaning of the

workplace, chairs before next patient walks in

- Ask patients and families to use hand sanitizer and practice good hand washing as soon as they enter the clinic.

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34 Non-Covid Facility

Non-covid facilities are responsible for provision of all the routine health check ups, follow ups and elective procedures in the community. Because of the ongoing Covid-19 pandemic, various private setups were not functioning to control the disease spread. With gradual unlocking the country, non-covid facilities are ready to function normally. However, if not taken the precautions well, they can stand responsible for the spread of the Covid-19 in the community. Hence it is very essential that infection prevention and control guidelines have been strictly followed at all the non-covid facilities. In the following chapters, we will be guiding about non-covid set up, what precautions to be taken, what to do if covid-19 case has been identified at the non-covid facility.

General guidelines for staff working at the Non covid facility:

- The non-covid facility can start functioning normally if it is clinically appropriate and essential. Also it should reach out proactively to clinically vulnerable patients and those whose care may have been delayed due to lockdown.
- Facility should have services of face-to-face consultation; however, try to prioritize the patient's issues and needs remotely and in advance when possible.
- Get the necessary equipment for online consultation and for patient triage.
- Use online consultations whenever you can. Make sure that video consultation can be availed to the patients whenever required.

- Educate staff members about the symptoms of Covid-19 infection, how to prevent the spread of the infection and how to follow basic infection prevention and control measures at all the time.

- Try to avail multidisciplinary approach for patient's betterment whenever needed; however, follow the basic social distancing and sanitization rules all the time while doing so.

- Educate patients about the importance and need of online consultation, how to use it in the time of need. Make the information accessible even to those patients who have limited digital knowledge.

- Cancel group health care activities (e.g., group therapy, recreational activities). Postpone elective procedures, surgeries, and non-urgent outpatient visits.

- Patients who require immediate attention should be prioritized over the follow up or routine health check patients.

- Elective surgeries which can be postponed without any clinical disadvantage for the patient, should be postponed.

- In case of emergency procedures, where there is no time to confirm the patient's non-covid status, treat the patient the same way assuming he has covid-19.

- Learn about the health issues which may have increased or have gone unnoticed during the lockdown period including mental health issues.

- You can support the patient's decision of self-care and self-management at home with adequate online guidance.

- Make referrals for further management as needed

- Patients without symptoms of COVID-19 who have booked for face-to-face consultation in advance should be called on the day of appointment and inquired about any new symptoms of covid-19.

- For elective surgeries, patients should be recommended to adhere to a strict protocol, that consists of a pre-quarantine period, followed by a triage visit and nasopharyngeal swab at the moment of hospitalization.

- For any face-to-face consultation of a patient who has come in contact with COVID-19 patient in the last 14 days, even if the patient does not themselves have relevant symptoms, Family Physician's staff should follow the standard operating procedures for patients with symptoms of COVID-19
- Try to solve all patient's doubts and manage care in a single consultation, to avoid the need for multiple visits to prevent patients as well as yourself from exposure to covid-19.
- Daily screening should be done when the patient arrives using a thermometer and pulse oximeter.
- Medical masks should be worn at all times while in the clinic.
- Educate the staff members about proper infection control procedures, including handwashing, good respiratory hygiene and proper use of personal protective equipment, including masks, gowns and gloves.

Fever and cough OPD:

- There should be a seperate entrance, waiting area as well as exit for the patients with chief complaints of covid like symptoms including cough, fever, difficulty in breathing etc.
- Recommend the staff members to safely separate patients with symptoms of COVID-19 from the other patient population.
- Dedicated staff members including nurses, on duty doctors and wardboys can be assigned for that OPD.
- The staff members working in the fever and cough OPD should follow proper infection prevention and control policies, hand washing strategies, good respiratory hygiene, should wear PPE consisting of a medical mask, gloves, face shield, goggles and gown or overall.
- Staff who have increased risk of covid-19 exposure should be identified and prophylactic management should be done.

- General guidelines for patients visiting the facility:
  - Patients should always wear a mask and gloves while entering the facility.
  - Patients who are showing symptoms of covid including cough, fever,

breathlessness, loss of taste and smell, should inform prior to the arrival.

- On arrival, avoid touching any surfaces, toys, magazines or books to prevent contracting the virus
- Use alcohol based sanitizer or soap and water to clean your hands
- If the patient has come in contact with a suspected or confirmed covid case, he should self quarantine for next 14 days and monitor closely for any symptoms of covid-19.

- **Social distancing:**
  - Limit the number of visitors accompanying patient
  - Limit the number of people in the elevators
  - Install glass or plastic dividers to separate the compartments in case there are more than one desks
  - Waiting room seating should be rearranged to maintain at least 6 feet distance
  - Schedule the appointments in such a way that the waiting time will be minimal and social distancing will be maintained in the waiting room, you can also ask the patients to wait outside or in their vehicles until their turn comes
  - The workplace should be well ventilated and avoid working in an airconditioned room
  - After delivering care, exit the room as quickly and directly as possible (i.e., complete documentation in the clean area).

Cleaning:

- Increase the frequency of cleaning and sanitization in the facility. Use alcohol based sanitizers (with at least 60%-70% alcohol) and diluted bleach solutions for cleaning.
- Bleach solution can be prepared by mixing 5 tablespoons of 5.25–8.25% bleach per gallon of water or 4 teaspoons of 5.25–8.25% bleach per quart of water. Water in use should be at the room temperature.

- Bleach solutions will be effective for disinfection up to 24 hours.
- Frequently clean the high-touch areas like door handles, elevator buttons and switches, telephones with 1% Sodium Hypochlorite Solution.
- Keep adequate spacing between two appointments to allow cleaning of the workplace, chairs before next patient walks in
- Ask patients and families to use hand sanitizer and practice good hand washing as soon as they enter the clinic.
- Provide no-touch waste containers with disposable liners in all reception, waiting, patient care, and restroom areas.

Actions to be taken if COVID-19 patient is identified in Non-covid facility-

- Inform the local authorities about the patient
- Assess the patient using all the safety precautions to determine the severity of the condition
- Make sure that the patient is immediately shifted to the isolated room
- If clinical status is stable, make arrangements for transferring the patient to Covid isolation facility.
- Follow all the infection prevention and control precautions while transportation of the patient
- Once the patient leaves the facility, follow all the disinfection guidelines for the hospital area as well as for the ambulance.
- All the contacts of the patients should be quarantined and monitored for the symptoms for the next 14 days.
- All the close HCW contacts of the patient should be put on prophylactic Hydroxychloroquine for the period of 7 weeks; make sure the contraindications for the treatment have been ruled out.

Decision on further/continued use of Non-covid facility where the Covid-19 case has been reported-

- Detailed risk assessment should be done, based on the number of cases

identified, number of patient visiting facilities, patients with chronic conditions etc.

- Facility can continue to function normally, if hospital authorities are sure that all the Covid-19 cases have been identified and isolated, the facility has been disinfected, all the suspects and contacts have been identified and quarantined.

- Despite taking all the precautions, if the hospital is still getting a number of suspects or cases identified and the primary source of infection remains undetected, non-covid facility can be converted into the covid facility.

Follow up actions-

- All the staff members and health care workers should be screened for any symptoms

- All the staff members should supervise themselves for any new symptoms of COVID-19

- Standard hygiene precautions should be followed very strictly

- Monitor all the admitted patients for any clinical symptoms for covid-19 or any other non-specific symptoms.

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35 Covid and Non-Covid Facility

Pandemics like the coronavirus disease (COVID)-19 can cause a significant strain on the healthcare system. Healthcare institutes must be ready with their backup plans for managing many patients with contagious infectious disease. Ideally, every large hospital is expected to have an area that can function as a high-level isolation unit. An isolation unit ensures that the healthcare staff and the hospital are equipped to deal with infectious disease outbreaks. Unfortunately, such facilities do not exist in several hospitals, especially in resource-limited settings. In such a scenario, healthcare setups need to convert their existing general structure into an infectious disease facility. In this chapter, we are mainly focusing on the basic principles and precautions needed to be followed in a Covid plus Non-Covid facility.

- **Education**

  - Provide detailed information about coronavirus disease 2019 (COVID-19), and why it is important to contain the outbreak to all of the staff members. Identify and separate the staff members who have volition to work under covid facility to control the disease outbreak.

  - Once segregated, the staff members who will be working in the covid facility including reception, admin, nurses and physicians should be provided with the proper training and guidance about how to prevent transmission of the disease.

  - Keep the staff informed on how to advise patients about changes in office procedures (e.g., calling prior to arrival if the patient has any signs of a respiratory infection and taking appropriate preventive actions) and

developing plans for management if they are exposed to COVID-19.

- Use of colour coded stripes to distinguish the patient from their exposure status can be done. For example, patients with no covid related symptoms, no travel or contact history can be given green wrist band, patients with fever or cough, or having positive contact history can be given red wrist bands.

- Educate the staff members about proper infection control procedures, including handwashing, good respiratory hygiene and proper use of personal protective equipment, including masks, gowns and gloves.

- Make sure the facility has The hospital infection control committee (HICC) who makes sure that all the infection prevention and control (IPC) strategies are being followed and all the staff members are following the safety instructions and policies.

IPC strategies

Strategies for preventing/limiting spread of COVID-19

1. Applying standard precautions for all patients at all times
2. Ensuring triage, early recognition and source control
3. Implementing empiric additional precautions for suspected cases of COVID-19 infection
4. Implementing administrative controls
5. Implementing environmental and engineering controls

1. Standard Precautions

The basic level of IPC precautions, to be always used for ALL patients regardless of suspected or confirmed status of the patient. Risk assessment is critical for all activities i.e. assess each health care activity and determine the personal protective equipment (PPE) that is needed for adequate protection.

Elements of Standard Precautions

a. Hand hygiene
b. Respiratory hygiene (cough etiquette)
c. PPE policies according to the exposure risk
d. Safe injection practices, sharps management and injury prevention
e. Safe handling, cleaning and disinfection of patient care equipment
f. Environmental cleaning

g. Safe handling and cleaning of soiled linen
h. Waste management

- **Office preparedness-**

Fig 1 - Red, Orange & Green Zone

The unit can be a standalone facility or can be housed in a tertiary healthcare facility with the equipment and capacity to care for critically ill patients.

Hospital facility can be divided into 3 distinct zones to prevent the infection spread-

Red zone- Patients with high or medium risk of COVID-19 infection are managed in the red zones. Red zones include the outdoor triage tents and the negative-pressure isolation room.

The red zone should have a separate group of healthcare workers to prevent cross infection with other areas, including regular cleaning staff. Personal protective equipment in the red zone should include a N95 mask covered by a surgical mask, hair cap, goggles or facial shield, gloves, gown, and shoe coverings.

It should have two seperate patient units

- The first one will be an isolation space for laboratory confirmed cases. Multiple patients can be kept in the same room.
- The second unit will be made for suspected cases which will include family and hospital contacts who are suspected to have potential contact with confirmed cases but await laboratory confirmation. This room will be built to include only one suspect per room.
- Separate rooms/Dormitory with in-house capacity of 5-10 beds/room is preferrable
- Each bed should be 1-2 meters (minimum 1 metre) apart from all sides from another one.

- Lighting, well-ventilation, heating, electricity, ceiling fan should be availed
- Potable water should be available
- Functional telephone system for providing communications should be present.
- Increase the frequency of cleaning and sanitization in the facility
- Frequently clean the high-touch areas like door handles, elevator buttons and switches, telephones
- Provide a dedicated equipment, like stethoscopes and digital thermometers, to be used in triage areas. Cleaning of the equipment should happen with appropriate cleaning solutions for each patient. Use of the use of disposable equipment can be considered when possible (e.g., blood pressure cuffs).

Yellow zone- Low-risk patients are managed in the yellow zones. Yellow zones include the indoor triage, waiting room, consultation rooms, observation rooms, and nursing station.

Health care workers in the yellow zones require less PPE (contact and droplet precaution: surgical mask, gown, gloves, eye protection). It is mandatory to follow the policies of infection prevention and control including hand hygiene, respiratory hygiene, social distancing, cleaning and sanitizing the area.

Green Zone- Green zones are used by healthcare providers (HCPs) for personal protective equipment (PPE) donning, inventory, planning, and dining. All patients are prohibited from entering the green zones.

No PPE is required in the green zones. Contaminated PPE should be removed before entering the green zones. Staff members working in the red zone should not be allowed in the green zone.

- **Fever and cough OPD**

  - There should be a seperate entrance and waiting area for the patients with chief complaints of covid like symptoms including cough, fever, difficulty in breathing etc.

  - Recommend the staff members to safely separate patients with symptoms of COVID-19 from the other patient population.

  - Dedicated staff members including nurses, on duty doctors and wardboys

can be assigned for that OPD.

- The staff members working in the fever and cough OPD should follow proper infection prevention and control policies, hand washing strategies, good respiratory hygiene, should wear PPE consisting of a medical mask, gloves, face shield, goggles and gown or overall.
- Staff who have increased risk of covid-19 exposure should be identified and prophylactic management should be done.

Securing entry and exit points-

Fig 2 - Non Touch Hand Sanitizer Dispenser

- The proper awareness and training on infection control measures should be provided to the Control room which is the first point of contact after entering the facility.
- A well informed and trained security guard to check and also should have a register for ins and outs and a designated nursing officer for checking proper PPE wear at the main entrance or at the gate.
- The international biohazard warning symbol and sign should be displayed on the doors of the rooms where suspects are kept,
- Only authorized & trained persons or those designated in work areas should be allowed to enter the examination areas.

- **Triage, Early Identification, and source Control**
  - -Develop a triage protocol for your practice based on patient and

community outbreak.

- Recommend that patients with respiratory symptoms and fever call the office before arrival.
- Implement alternative patient flow systems.
- Waiting room seating should be rearranged to maintain at least 6 feet distance
- Consider arranging a separate entrance for symptomatic patients.
- Provide no-touch waste containers with disposable liners in all reception, waiting, patient care, and restroom areas.
- Provide alcohol-based hand rub and masks in all reception, waiting, patient care, and restroom areas for patients with respiratory symptoms. Always keep soap dispensers stocked with handwashing signs.
- Discontinue the use of toys, magazines, and other shared items in waiting areas, as well as office items shared among patients, such as pens, clipboards, phones, etc.
- Use clinical triage in all health care facilities for early identification of patients with acute respiratory infection (ARI) to prevent transmission of pathogens to health care workers and others.

i. Prevent overcrowding
ii. Conduct rapid triage
iii. Family members should wait outside the triage area
iv. Place ARI patients in dedicated waiting areas with adequate ventilation
v. Ask patients with respiratory symptoms to wear face mask, follow respiratory and hand hygiene
vi. Ensure at least 1 m distance between patients
vii. Maintain a one-way flow of patients and staff
viii. In addition to standard precautions, implement: Droplet precautions, Contact precautions (if close contact with the patient or contaminated equipment or surfaces/materials)
ix. Equipment in triage area:

The triage or screening area should have-

a) Clear directions to triage area
b) Algorithm for triage
c) Screening questionnaire
d) Documentation papers
e) PPE
f) Hand hygiene equipment
g) IEC materials and IPC posters
h) Infrared thermometer
i) Waste bins and access to cleaning/ disinfection
j) Signage in local language for patients with specific symptoms to alert HCWs

- **Standard hygiene-**

A. General instructions.

1. Lint-free dusters/ mops should be used; and washed with soap and water after every use, disinfected/ discarded as applicable. Always put Caution signage before cleaning.
2. Brooms are not to be used in the hospital.
3. The three-bucket technique should be used on every floor to facilitate hygienic cleaning of the environment.
4. All cleaning activities to be done with donned PPE as applicable.
5. All cleaning and disinfection equipment of the Isolation and Triage area must remain in isolation and triage area strictly.
6. Cleaning and disinfection of other clinical areas, as per the HIC policy.

B. Cleaning and disinfection techniques and supplies

1. Cleaning should progress from the least soiled (cleanest) to the most soiled (dirtiest) areas, and from the higher to lower levels so that debris may fall on the floor and is cleaned last
2. Dedicated cleaning instruments to be used in the Isolation area.
3. New cloth/ duster to be used for each patient admission and to be discarded after cleaning.
4. Terminal cleaning to be done on discharge, transfer, or death of the patient. (All mops head, dusters and clothes to be discarded after the terminal cleaning and disinfecting)
5. It is recommended to use a freshly prepared solution on a daily basis or for each cleaning shift. Buckets should be washed with detergent, rinsed, dried and stored inverted to drain fully when not in use.
6. Frequently touched areas like tabletops, chair handles, pens, diary files,

keyboards, mouse, mouse pad, tea/coffee dispensing machines etc. should specially be cleaned.

7. For metallic surfaces like door handles, security locks, keys etc. 70% alcohol can be used to wipe down surfaces where the use of bleach is not suitable.
8. If someone is coughing, without following respiratory etiquettes or mask, the areas around his/her seat should be vacated and cleaned with 1% sodium hypochlorite.
9. 70% Alcohol can be used to wipe down surfaces where the use of bleach is not suitable, e.g. metal.
10. Remove PPE, discard in the appropriate yellow/ Red bio medical waste disposal bag as applicable and wash hands with soap and water.

C. Housekeeping in the isolation room and triage area.

1. Before admission: The admitting physician should inform the sister in-charge of isolation ward at least one hour before admission, mentioning the diagnosis, sex and the general state of the patient.
2. Cover the mattress and pillows with an impervious disposable cover.
3. Separate urinals, bedpans and thermometers/ BP apparatus are to be used for each patient.
4. Bins lined with the appropriate color-coded plastic liner should be available in each room for disposal of biomedical waste.
5. Rooms should be well lit, and isolated according to disease conditions.

D. Cleaning procedure for isolation room:

1. FULL PPE KIT to be donned before entering the isolation/ triage area. Linen should be stripped from the bed with care taken not to shake the linen during this action.
2. All other articles such as IV stands and furniture should be cleaned with detergent and disinfected followed by high-level disinfectant.
3. Walls should be cleaned with detergent and mopped with a high-level disinfectant.
4. The bathrooms should be cleaned with detergent and water followed by disinfection with hypochlorite 1:50 dilution.

E. At discharge (terminal disinfection):

a. The pillows and mattress cover (only Disposables to be used) and disposed in yellow bag) (Steps to be followed only in dire shortage/ or

upon instructions: Covers are to be cleaned with detergent, disinfected with a high-level disinfectant contact time of 1 hour and sent to the laundry)

b. Bed sheets, curtains, gowns and dusters (only Disposables to be used and disposed in yellow bag) (Steps to be followed only in dire shortage/ or upon instructions: it must be removed, soaked in with a high-level disinfectant for one hour and then sent to laundry)

c. After disinfection, wash the room, wall, window, doors, bathroom, sink and furniture with soap solution after doing thorough high dusting in that cubicle.

d. Soak bed pan, urinal, kidney basin in with a high-level disinfectant for one hour, wash with detergent and dry it under sunlight.

e. Bath basin, multi-bin, bucket, jugs, mugs are washed with soap solution and dried in sunlight.

f. Rubber sheets (only Disposables to be used and disposed of in Red Bag) (Steps to be followed only in dire shortage/ or upon instructions: (Mackintosh) are to be cleaned with detergent and water, dried, powdered and replaced.)

6. All disposables to be packed in the appropriate Bio medical waste disposal bags and labelled. (Steps to be followed only in dire shortage/ or upon instructions: The person carrying used linen in the trolleys should inform others before carrying, and they may move aside to give way for these trolleys.)

F. Environmental cleaning and surface disinfection, while patient is admitted:

1. Disinfectants: 1% Sodium hypochlorite freshly prepared, contact time of at least 10 mins. 70% alcohol: Isopropyl or ethyl alcohol: for delicate instruments (Thermometer, BP Cuffs, Stethoscope, Metal surfaces)
2. Apply disinfectant to surface using damp cloth in steady sweeping motion, do not spray/ splash (uneven coverage, aerosol generation)
3. Mop the floor and wipe down all accessible surfaces of floor, furniture, fittings, tabletops, windows, bed and mattress with 1% sodium hypochlorite. (From clean to dirty area)
4. Wipe all high touch surfaces with 1% sodium hypochlorite or 70% alcohol.
5. Discard cloth, absorbent cleaning material into double bagged biohazard bags after cleaning and disinfecting each area, fasten the bags with cable ties.

6. Disinfect the bucket by soaking in 1% sodium hypochlorite.

G. Frequency of cleaning surface:

a. High touch surfaces: Doorknobs, telephone, call bells, handles, chair rests, stair rails, light switches, wall areas around toilets should be cleaned every 1-2 hourly in clinical areas and 3-4 hourly in non-clinical areas.

H. Precautions to take after completing cleaning and disinfection:

1. Staff to wash hands with soap and water after removing the PPE.
2. Discard all PPE in double bagged biohazard bags, which should be labelled and sealed.
3. Staff should immediately report to a medical officer incase of symptoms due to occupational exposure.

- **Social distancing**
  - Limit the number of visitors accompanying patient
  - Limit the number of people in the elevators
  - Schedule the appointments in such a way that the waiting time will be minimal and social distancing will be maintained in the waiting room, you can also ask the patients to wait outside or in their vehicles until their turn comes
  - After delivering care, exit the room as quickly and directly as possible (i.e., complete documentation in the clean area).
  - Ensure adherence to standard precautions, including airborne precautions and use of eye protection. Educate about proper donning and doffing methods of personal protective equipment(PPE).

Principles of PPE Use:
Always perform hand hygiene before and after wearing PPE:

i. PPE should be available where and when indicated according to risk in the correct size
ii. Always put PPE on before contact with the patient
iii. Remove PPE immediately after completing the task and/or leaving the patient care area
iv. Never reuse disposable PPE
v. PPE kits to be donned and doffed under observation in the specified area only.

vi. Change PPE immediately if it becomes soiled/ contaminated or damaged
vii. PPE should not be adjusted or touched during patient care
viii. Never touch your face while wearing PPE
ix. If there is concern and/or breach of these practices leave the patient care area when safe to do so properly remove and change the PPE. (INFORM the MEDICAL OFFICER about Breach of PPE/ Exposure, for Post exposure measures Immediately)
x. Always remove PPEs remove carefully to avoid self-contamination
xi. From dirtiest to cleanest areas
xii. Always enter donned with full compliant PPE kit in the demarcated
xiii. Do not reuse PPE in the ISOLATION, Triage area.

- **Food facility-**

Guidelines for canteen employees-

- Employee to maintain a distance of 1 meter from each other
- Employee to wear masks at all times
- Coughing and sneezing etiquette needs to be followed by sneezing/coughing into the elbow or using tissues and immediately discarding it in the waste after use.
- Employees with runny noses and cough must be asked to remain absent from work till they are completely devoid of symptoms.
- Employee to wear gloves while procuring food supplies. Employees must follow the correct hand washing protocol after touching such material. Employees must avoid touching their face and eyes.
- Hair, nails, and moustache/ beard must be properly trimmed and hair must be tied
- Sanitizers must be provided for all employees and it must be used in the time but not during Food preparation.
- Employees must not wear watch or jewelry. Instruments like mobile should be discouraged while at work place or should be sanitized frequently.
- Uniform must be changed daily and provision must be made to supply clean uniform
- Daily.
- Footwear: dedicated footwear is to be used in kitchens.
- No one apart from staff working to enter the kitchen.

- **Screening for infectious diseases (enteric, respiratory or skin infection)**

- All food handlers must undergo medical examination by a registered medical practitioner and must be free from infectious and transmissible diseases.
- Employees should report the following conditions to the supervisor for possible exclusion from food handling areas—jaundice, vomiting, diarrhoea, fever, sore throat with fever, visibly infected lesions, boils, cuts, sores and discharge from ears/eyes/ nose, etc. (Personnel with open cuts, wounds or burns shall be required to cover them with suitably waterproof dressings before starting operation.)

- **Kitchen Procedures**

Pre-preparation

- Pre preparation area must be well segregated in to dry and wet areas.
- All contact surfaces must be pre-sanitized.
- All vegetables will be washed with salt water or vinegar water thoroughly before use.

- **Storage facilities**

- There must be adequate storage facilities for all items including food ingredients, equipment, and non-food materials such as utensils, linen, single service and single-use articles, packaging and chemical agents.

- During storage, food items must be protected from contamination such as water leakage, pest infestation or any other insanitary condition.

- Adequate off-the floor shelves and racks must be used for storing food. Floors should not be used for storing food.

- The storage area must be cleanable and in a dry location to prevent deterioration. It should be protected from pests and should be away from locker rooms, toilets, sewer lines, stores of chemicals/ pesticides.

- The storage facilities should be designed and constructed to avoid cross contamination.

- Cold storage at 4 °C–8 °C and freezer at −18 °C should be provided for foods that need refrigeration and for frozen foods, with a separate refrigerator and freezer for vegetarian and non-vegetarian products.

- Separate storage sections should be provided for raw, processed,

packaging, rejected, returned or recalled food items. Allergen material or foods like groundnuts must be distinguishably marked.

- Cleaning agents should have prominent labels and stored separately.

- **Food temperature**

  - Cold food items are refrigerated and maintained at 4 °C–8 °C or below.
  - Walk-in storage facilities are maintained at the following temperatures and the temperatures are checked daily and a log is maintained of the temperatures.
  - Foods prepared to be served cold are cooled from their preparation temperature to 4 °C or below. - The cooling period should not exceed 4 hours.
  - Hot foods are held at an internal temperature of 63 °C or above.
  - Both hot and cold food items should be transported in food trolleys in such a manner that appropriate temperatures are maintained during the transportation of the food.

- **Food type Temperature**

  - Frozen food −18 °C
  - Cooked food Above 60 °C
  - Cold food Below 5 °C
  - Dry stores At room temperature

- **Food Distribution**

  - Wearing Face mask And gloves during food distribution and service - during portioning, packing, and during food service to patients and health care personnel is compulsory.
  - Avoid touching your face and eyes, use sanitizers as appropriate and practice correct hand washing protocols at intervals.
  - Trays should be kept covered when food is served in the ward.
  - All eating and drinking utensils and food contact surfaces must be clean and Sanitized before use.
  - Split Meal timings to avoid crowds in the canteen area.
  - Tables to be placed at a distance of 1 meter and social distancing to be practiced.

- Use of disposable food service utensils and cutlery can be considered.

- **Cleaning Utensils and sanitization**

  - Food storage and preparation areas are to be sanitized regularly.
  - Doors, handles, doorknobs, light switches, trolley jacks, work benches, equipment must be cleaned and sanitized frequently.
  - People cleaning should wear masks and gloves.
  - Dishes and eating utensils must be washed and cleaned as per standard procedures.
  - The returned trays should be heat treated to render the items sanitized (wash temperature 65 °C–70 °C, rinse temperature 85 °C–95 °C)
  - Wear gloves, masks when handling patient trays, dishes and utensils.
  - Disposal of waste from the kitchen
  - Dietary wastes should be kept in bins lined by black plastic bags outside the kitchen department, which are removed regularly.
  - Waste stores and dustbins must be kept appropriately clean, free of pests and in closed conditions and should be disposed of as per local rules and regulations including those for plastic and other non-environment-friendly materials.

- **Additional precautions**

  i. Cohort HCWs to exclusively care for cases to reduce the risk of spreading transmission.

  ii. Place patient beds at least 1m apart.

  iii. Perform procedures in an adequately ventilated room; i.e. at least natural ventilation with at least 160 l/s/patient air flow or negative pressure rooms with at least 12 air changes per hour (ACH) and controlled direction of air flow when using mechanical ventilation.

  iv. Limit the number of persons present in the room to the absolute minimum required for the patient's care and support.

  v. Use either single use disposable equipment or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use (e.g. ethyl alcohol 70%);

vi. Refrain from touching eyes, nose or mouth with potentially contaminated hands; Some aerosol generating procedures have been associated with increased risk of transmission of coronaviruses such as tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation and bronchoscopy.

vii. Ensure that HCWs performing aerosol-generating procedures use PPE with particulate respirator at least as protective as a NIOSH-certified N95, EU FFP2 or equivalent. When putting on a disposable particulate respirator, always perform the seal-check. Note that if the wearer has facial hair (beard) this can prevent a proper respirator fit.

viii. Avoid the movement and transport of patients out of the room or area unless medically necessary.

ix. Use designated portable X-ray equipment and/or other important diagnostic equipment.

x. If transport is required, use predetermined transport routes to minimize exposures to staff, other patients and visitors and apply medical mask to patient; Ensure that HCWs who are transporting patients wear appropriate PPE as per policy on PPE usage and perform hand hygiene;

xi. Notify the receiving area of necessary precautions as soon as possible before the patient's arrival;

xii. Routinely clean and disinfect patient-contact surfaces;

xiii. Limit the number of HCWs, family members and visitors in contact with a patient with suspected 2019 nCoV- Acute Respiratory Disease;

xiv. Maintain a record of all persons entering the patient's room including all staff and visitors.

xv. Duration of contact and droplet precautions for 2019 nCoV- Acute Respiratory Disease Standard precautions should always be applied at all times. Additional contact and droplet precautions should continue until the patient is asymptomatic.

xvi. Separate lift to be used for transport of Suspects, Covid-19 patients.

xvii. Separate floors to be assigned for suspects.

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36 Dedicated Covid Hospitals

The Dedicated Covid Hospital (DCHC) and covid care centers(CCC) must be a self-contained establishment that can meet most of its daily needs with only essential but limited contact with the outside world.

Basic requirements the facility should have are as follows-

- Continuous safe water supply
- Appropriate cleaning practices
- Adequate floor space for beds
- Appropriate hand washing facilities
- Adequate ventilation for isolation rooms and procedure rooms
- Adequate isolation facilities should be available
- Regulated and rational traffic flow to minimize exposure of high-risk patients and facilitate patient and clinical material transport
- Precautions to control rodents, pests and other vectors
- Appropriate waste management facilities/ practices.

The unit can be a standalone facility or can be housed in a tertiary healthcare facility with the equipment and capacity to care for critically ill patients.

Hospital facility can be divided into 3 distinct zones to prevent the infection spread-

Red zone- Patients with high or medium risk of COVID-19 infection are managed in the red zones. Red zones include the outdoor triage tents and the negative-pressure isolation room.

The red zone should have a separate group of healthcare workers to prevent cross infection with other areas, including regular cleaning staff. Personal protective equipment in the red zone should include a N95 mask covered by a surgical mask, hair cap, goggles or facial shield, gloves, gown, and shoe coverings.

It should have two seperate patient units

- The first one will be an isolation space for laboratory confirmed cases. Multiple patients can be kept in the same room.
- The second unit will be made for suspected cases which will include family and hospital contacts who are suspected to have potential contact with confirmed cases but await laboratory confirmation. This room will be built to include only one suspect per room.
- Separate rooms/Dormitory with in-house capacity of 5-10 beds/room is preferrable
- Each bed should be 1-2 meters (minimum 1 metre) apart from all sides from another one.
- Lighting, well-ventilation, heating, electricity, ceiling fan should be availed
- Potable water should be available
- Functional telephone system for providing communications should be present.
- Increase the frequency of cleaning and sanitization in the facility
- Frequently clean the high-touch areas like door handles, elevator buttons and switches, telephones
- Provide a dedicated equipment, like stethoscopes and digital thermometers, to be used in triage areas. Cleaning of the equipment should happen with appropriate cleaning solutions for each patient.

Yellow/Orange zone- Low-risk patients are managed in the yellow zones. Yellow zones include the indoor triage, waiting room, consultation rooms, observation rooms, and nursing station.

Health care workers in the yellow zones require less PPE (contact and droplet precaution: surgical mask, gown, gloves, eye protection). It is mandatory to follow the policies of infection prevention and control including hand hygiene, respiratory hygiene, social distancing, cleaning and sanitizing the area.

Green Zone- Green zones are used by healthcare providers (HCPs) for personal protective equipment (PPE) donning, inventory, planning, and dining. All

patients are prohibited from entering the green zones.

No PPE is required in the green zones. Contaminated PPE should be removed before entering the green zones. Staff members working in the red zone should not be allowed in the green zone.

- **Securing entry and exit points-**

  - The proper awareness and training on infection control measures should be provided to the Control room which is the first point of contact after entering the facility.
  - A well informed and trained security guard to check and also should have a register for ins and outs and a designated nursing officer for checking proper PPE wear at the main entrance or at the gate.
  - The international biohazard warning symbol and sign should be displayed on the doors of the rooms where suspects are kept,
  - Only authorized & trained persons or those designated in work areas should be allowed to enter the examination areas.
  - Doors of the covid positive patient's room should be closed at all times
  - There should be a double door entry that was managed with only one door to be open at a single time.
  - Non-touch sanitizer dispensers should be made available at all the entry and exit points to prevent cross infection.

- **Standard hygiene**

Policy for environmental cleaning and disinfection in the DCH (Red zone and Orange zone).

A. General instructions.

1. Lint-free dusters/ mops should be used; and washed with soap and water after every use, disinfected/ discarded as applicable. Always put Caution signage before cleaning.
2. Brooms are not to be used in the hospital.
3. The three-bucket technique should be used on every floor to facilitate hygienic cleaning of the environment.
4. All cleaning activities to be done with donned PPE as applicable.
5. All cleaning and disinfection equipment of the Isolation and Triage area must remain in isolation and triage area strictly.
6. Cleaning and disinfection of other clinical areas, as per the HIC policy.

B. Cleaning and disinfection techniques and supplies

1. Cleaning should progress from the least soiled (cleanest) to the most soiled (dirtiest) areas, and from the higher to lower levels so that debris may fall on the floor and is cleaned last
2. Dedicated cleaning instruments to be used in the Isolation area.
3. New cloth/ duster to be used for each patient admission and to be discarded after cleaning.
4. Terminal cleaning to be done on discharge, transfer, death of the patient. (All mops head, dusters and clothes to be discarded after the terminal cleaning and disinfecting as per BMWD guidelines) (Refer Annexure III. Policy on Biomedical waste disposal)
5. It is recommended to use a freshly prepared solution on a daily basis or for each cleaning shift. Buckets should be washed with detergent, rinsed, dried and stored inverted to drain fully when not in use.
6. Frequently touched areas like tabletops, chair handles, pens, diary files, keyboards, mouse, mouse pad, tea/coffee dispensing machines etc. should specially be cleaned.
7. For metallic surfaces like door handles, security locks, keys etc. 70% alcohol can be used to wipe down surfaces where the use of bleach is not suitable.
8. If someone is coughing, without following respiratory etiquettes or mask, the areas around his/her seat should be vacated and cleaned with 1% sodium hypochlorite.
9. 70% Alcohol can be used to wipe down surfaces where the use of bleach is not suitable, e.g. metal.
10. Remove PPE, discard in the appropriate yellow/ Red bio medical waste disposal bag as applicable and wash hands with soap and water.

C. Housekeeping in the isolation room and triage area.

1. Before admission: The admitting physician should inform the sister in-charge of isolation ward at least one hour before admission, mentioning the diagnosis, sex and the general state of the patient.
2. Cover the mattress and pillows with an impervious disposable cover.
3. Separate urinals, bedpans and thermometers/ BP apparatus are to be used for each patient.
4. Bins lined with the appropriate color-coded plastic liner should be available in each room for disposal of biomedical waste.
5. Rooms should be well lit, and isolated according to disease conditions.

D. Cleaning procedure for isolation room:

1. (FULL PPE KIT to be donned before entering the isolation/ triage area)Linen should be stripped from the bed with care taken not to shake the linen during this action.
2. All other articles such as IV stands and furniture should be cleaned with detergent and disinfected followed by high-level disinfectant.
3. Walls should be cleaned with detergent and mopped with a high-level disinfectant.
4. The bathrooms should be cleaned with detergent and water followed by disinfection with hypochlorite 1:50 dilution.

E. At discharge (terminal disinfection):

a. The pillows and mattress cover (*ONLY Disposables to be used) and disposed in yellow bag) (Steps to be followed only in dire shortage/ or upon instructions:
   Covers are to be cleaned with detergent, disinfected with a high-level disinfectant contact time of 1 hour and sent to the laundry)
b. Bed sheets, curtains, gowns and dusters (*ONLY Disposables to be used and disposed in yellow bag) (Steps to be followed only in dire shortage/ or upon instructions: it must be removed, soaked in with a high-level disinfectant for one hour and then sent to laundry)
c. After disinfection, wash the room, wall, window, doors, bathroom, sink and furniture with soap solution after doing thorough high dusting in that cubicle.
d. Soak bed pan, urinal, kidney basin in with a high-level disinfectant for one hour, wash with detergent and dry it under sunlight.
e. Bath basin, multi-bin, bucket, jugs, mugs are washed with soap solution and dried in sunlight.
f. Rubber sheets (only Disposables to be used and disposed in Red Bag) (Steps to be followed only in dire shortage/ or upon instructions: (Mackintosh) are to be cleaned with detergent and water, dried, powdered and replaced.)
6. All disposables to be packed in the appropriate Bio medical waste disposal bags and labelled. (Steps to be followed only in dire shortage/ or upon instructions: The person carrying used linen in the trolleys should inform others before carrying, and they may move aside to give way for these trolleys.)

F. Environmental cleaning and surface disinfection, while patient is admitted:

1. Disinfectants: 1% Sodium hypochlorite freshly prepared, contact time of at least 10 mins. 70% alcohol: Isopropyl or ethyl alcohol: for delicate instruments (Thermometer, BP Cuffs, Stethoscope, Metal surfaces)
2. Apply disinfectant to surface using damp cloth in steady sweeping motion, do not spray/ splash (uneven coverage, aerosol generation)
3. Mop the floor and wipe down all accessible surfaces of floor, furniture, fittings, tabletops, windows, bed and mattress with 1% sodium hypochlorite. (From clean to dirty area)
4. Wipe all high touch surfaces with 1% sodium hypochlorite or 70% alcohol.
5. Discard cloth, absorbent cleaning material into double bagged biohazard bags after cleaning and disinfecting each area, fasten the bags with cable ties.
6. Disinfect the bucket by soaking in 1% sodium hypochlorite.

G. Frequency of cleaning surface:

High touch surfaces: Doorknobs, telephone, call bells, handles, chair rests, stair rails, light switches, wall areas around toilets should be cleaned every 1-2 hourly in clinical areas and 3-4 hourly in non-clinical areas.

H. Precautions to take after completing cleaning and disinfection:

1. Staff to wash hands with soap and water after removing the PPE.
2. Discard all PPE in double bagged biohazard bag, which should be labelled and sealed.
3. Staff should immediately report to medical officer incase of symptoms due to occupational exposure.

Implementing environmental and engineering controls

a. Preferably patient should be in a single room
b. Natural ventilation with air flow of at least 160 L/s per patient (or) Negative pressure rooms with at least 12 air changes (ACH) per hour
c. Controlled direction of air flow when using mechanical ventilation
d. Cohort: All patients with respiratory illness should be in a single room or minimum 1m away from other patients when waiting for a room

- **Food facility-**

Guidelines for canteen employees-

- Employee to maintain a distance of 1 meter from each other
- Employee to wear masks at all times
- Coughing and sneezing etiquette needs to be followed by sneezing/coughing into the elbow or using tissues and immediately discarding it in the waste after use.
- Employees with runny noses and cough must be asked to remain absent from work till they are completely devoid of symptoms.
- Employee to wear gloves while procuring food supplies. Employees must follow the correct hand washing protocol after touching such material. Employees must avoid touching their face and eyes.
- Hair, nails, and moustache/ beard must be properly trimmed and hair must be tied
- Sanitizers must be provided for all employees and it must be used in the time but not during Food preparation.
- Employees must not wear watch or jewelry. Instruments like mobile should be discouraged while at work place or should be sanitized frequently.
- Uniform must be changed daily and provision must be made to supply clean uniform Daily.
- Footwear: dedicated footwear is to be used in kitchens.
- No one apart from staff working to enter the kitchen.

- **Screening for infectious diseases (enteric, respiratory or skin infection)**

  - All food handlers must undergo medical examination by a registered medical practitioner and must be free from infectious and transmissible diseases.
  - Employees should report the following conditions to the supervisor for possible exclusion from food handling areas—jaundice, vomiting, diarrhoea, fever, sore throat with fever, visibly infected lesions, boils, cuts, sores and discharge from ears/eyes/ nose, etc. (Personnel with open cuts, wounds or burns shall be required to cover them with suitably waterproof dressings before starting operation.)

  - **Kitchen Procedures**
  - **Pre-preparation**
  - Pre preparation area must be well segregated in to dry and wet areas.
  - All contact surfaces must be pre-sanitized.
  - All vegetables will be washed with salt water or vinegar water thoroughly before use.

- **Storage facilities**

  - There must be adequate storage facilities for all items including food ingredients, equipment, and non-food materials such as utensils, linen, single service and single-use articles, packaging and chemical agents.
  - During storage, food items must be protected from contamination such as water leakage, pest infestation or any other insanitary condition.
  - Adequate off-the floor shelves and racks must be used for storing food. Floors should not be used for storing food.
  - The storage area must be cleanable and in a dry location to prevent deterioration. It should be protected from pests and should be away from locker rooms, toilets, sewer lines, stores of chemicals/ pesticides.
  - The storage facilities should be designed and constructed to avoid cross contamination.
  - Cold storage at 4 °C–8 °C and freezer at −18 °C should be provided for foods that need refrigeration and for frozen foods, with a separate refrigerator and freezer for vegetarian and non-vegetarian products.
  - Separate storage sections should be provided for raw, processed, packaging, rejected, returned or recalled food items. Allergen material or foods like groundnuts must be distinguishably marked.
  - Cleaning agents should have prominent labels and stored separately.

- **Food temperature**

  - Cold food items are refrigerated and maintained at 4 °C–8 °C or below.
  - Walk-in storage facilities are maintained at the following temperatures and the temperatures are checked daily and a log is maintained of the temperatures.
  - Foods prepared to be served cold are cooled from their preparation temperature to 4 °C or below. - The cooling period should not exceed 4 hours.
  - Hot foods are held at an internal temperature of 63 °C or above.
  - Both hot and cold food items should be transported in food trolleys in such a manner that appropriate temperatures are maintained during the transportation of the food.

- **Food type Temperature**

  - Frozen food −18 °C
  - Cooked food Above 60 °C
  - Cold food Below 5 °C

- Dry stores At room temperature

- **Food Distribution**

  - Wearing Face mask And gloves during food distribution and service - during portioning, packing, and during food service to patients and health care personnel is compulsory.
  - Avoid touching your face and eyes, use sanitizers as appropriate and practice correct hand washing protocols at intervals.
  - Trays should be kept covered when food is served in the ward.
  - All eating and drinking utensils and food contact surfaces must be clean and Sanitized before use.
  - Split Meal timings to avoid crowds in the canteen area.
  - Tables to be placed at a distance of 1 meter and social distancing to be practiced.
  - Use of disposable food service utensils and cutlery can be considered.

- **Cleaning Utensils and sanitization**

  - Food storage and preparation areas are to be sanitized regularly.
  - Doors, handles, doorknobs, light switches, trolley jacks, work benches, equipment must be cleaned and sanitized frequently.
  - People cleaning should wear masks and gloves.
  - Dishes and eating utensils must be washed and cleaned as per standard procedures.
  - The returned trays should be heat treated to render the items sanitized (wash temperature 65 °C–70 °C, rinse temperature 85 °C–95 °C)
  - Wear gloves, masks when handling patient trays, dishes and utensils.
  - Disposal of waste from the kitchen
  - Dietary wastes should be kept in bins lined by black plastic bags outside the kitchen department, which are removed regularly.
  - -Waste stores and dustbins must be kept appropriately clean, free of pests and in closed conditions and should be disposed of as per local rules and regulations including those for plastic and other non-environment-friendly materials.

- **Operation theatre/room-**

  - Materials or objects not essential for the operation (e.g. pens, telephones, keys) should remain outside the SARS-CoV-2 operating area.

- Entering and leaving the operating room should be kept to an absolute minimum.
- The patient should be followed up in the operating room and then transferred directly to the SARS-CoV-2 surgical ward.
- The patient's route between the operating room and the ward should be covered as quickly and directly as possible and has priority over other transport.
- If it is clinically appropriate then recommendation is to make him wear a surgical mask when in the corridors
- A detailed list of the staff members involved in the surgical intervention should be made, in order to guarantee disease monitoring.

Patient transport and stay:

- The movement of patients should be minimized within the hospital premises.
- If such transport is necessary, patients must don either medical masks or particulate respirators, whichever is available.
- The area to which they are being transported should be alerted about their arrival.
- A separate corridor should be preferred.
- In case the patients meet any surfaces, they must be disinfected.
- For mapping the patient transfer, the path of transport and specific elevators should be identified.

Transporting of diseased patients-

- When transferring the dead bodies all tubings attached to the bodies, such as nasogastric tubes, Foley catheter, and any others, are to be removed, keeping biosafety in place. All orifices are to be cleaned and disinfected and plugged to prevent any fluid leakage. All wounds must be redressed after disinfection with impermeable dressings. All PPE must be removed immediately, and hand hygiene must be performed immediately.

Guidelines for health care workers

i. Healthcare workers in different settings of hospitals shall use PPEs appropriate to their risk profile as detailed in the guidelines issued by this Ministry (available at:

ii. All healthcare workers should undergo training on Infection Prevention and Control and should have information about common

signs and symptoms, need for self-health monitoring and need for prompt reporting of symptoms if they develop any.

iii. Provision of daily (thermal) screening of all hospital staff should be availed

Iv. All healthcare workers managing COVID-19 cases should be provided with prophylactic management under medical supervision.

Fig 1, 2 - Hand Wash, Infrared Thermometer

PPE use:

Personal protective equipment (PPE) is a combination of protective gears designed to safeguard the health of workers by minimising the exposure to a biological agent.

PPE consists of goggles/ face-shield, mask, gloves, coverall/gowns (with or without aprons), head cover and shoe cover.

The use of triple layer medical mask and latex examination gloves, besides following social distancing guidelines and frequent use of hand sanitiser over gloves has been recommended by WHO.

Education on proper donning and doffing of the PPE kit should be provided.

Separate donning and doffing areas:

- Ensure that areas for donning and doffing are designated as separate from the patient care area and one-way flow from the donning area to the patient care area to the doffing area should be maintained.
- Confirm that the doffing area is large enough to allow freedom of movement for safe doffing as well as have a space for waste material collection, a new glove supply, and ABHR used during the doffing process.

Facilities should ensure that space and layout allow for clear separation between clean and contaminated areas. The direction of flow should be marked (e.g., signs on the floor) with visible signage; temporary plastic enclosures can be added if necessary.

Post signage to highlight key aspects of PPE donning and doffing, including:

- Designating clean areas vs. contaminated areas
- Reminding healthcare workers to wait for a trained observer before removing PPE
- Listing each step of the doffing procedure
- Reinforcing the need for slow and deliberate removal of PPE to prevent self-contamination
- Reminding healthcare workers to disinfect gloved hands in between steps of the doffing procedure, as indicated below.

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Section I

Miscellaneous

37 Oxygen Therapy and Other Novel Equipments Used For Patient Care

A high number of patients with severe COVID-19 disease develop acute respiratory distress syndrome (ARDS) and require respiratory support. In Covid-19, usually patients come with a characteristic of Type 1 respiratory failure (T1RF), in which there is hypoxia (PaO2<8kPa), without hyper-capnia (carbon dioxide retention or PaCO2). Common presentation is worsening hypoxia, with additional signs such as tachypnoea, increased use of accessory muscles,tachycardia, pale and cold peripheries, sweating, confusion,agitation or reduced level of consciousness and cyanosis.

Hence, it is important to have knowledge about various oxygen delivery systems, non invasive and invasive ventilation methods, as well as other equipment which are used in medical set up.

Oxygen delivery system:

Oxygen delivery system is a device which is used to administer, regulate and supplement oxygen to a subject to increase the arterial oxygenation.

Low dependency system

-Variable performance devices / low flow devices
-Fixed performance devices / high flow devices

Low flow oxygen devices

- Cannot deliver constant FiO2.
- Oxygen flow rate is upto 6 - 8 L/min

- Delivers mixture of oxygen + room air
- Eg : Nasal cannula, oxygen masks, mask with reservoir bags etc

High flow oxygen devices

- Maintain constant FiO2
- Delivering O2 at very high flow
- Flow usually 4 times the actual Minute volume
- Eg : jet-mixing venturi masks, reservoir nebuliser, oxygen blender

Common Low flow devices:

- Nasal cannula (prongs or spectacles)
- Nasal catheters
- Transtracheal catheter
- Face mask
- Partial rebreathing mask
- Non rebreathing mask
- Tracheostomy mask

1.Nasal cannula

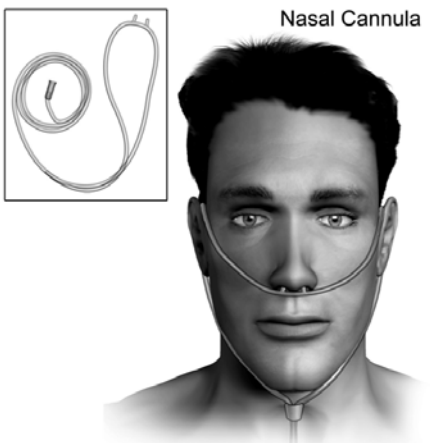

Fig 1 - Nasal Canula

2. Consists of 2 soft prongs attached to O2 supply tubing

- A flow rate of 2–4 L/min delivers an FiO2 of 0.28–0.36 respectively
- FiO2 = 20% + (4 × oxygen litre flow)
- No increase in FiO2 if flow is more than 6L/min
- Nasopharynx acts as a reservoir

- If patient breathes through mouth, air flow produces a Venturi effect in the posterior pharynx entraining oxygen from the nose
- Available in different sizes and different prong shapes

Advantages:

- Ideal for patients on long-term oxygen therapy
- Lightweight and comfortable
- The patient is able to speak, eat and drink
- Humidification not required
- Low cost

Disadvantages:

- Can not provide high flow O2
- Irritation and can not be used in nasal obstruction
- FiO2 varies with respiratory efforts
- High flow rates are uncomfortable

3. Nasal catheter

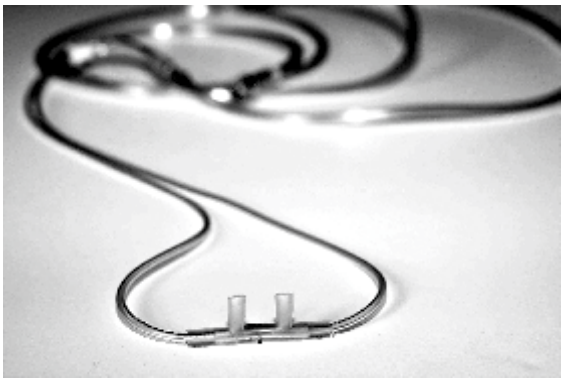

Fig 2 - Nasal Catheter

Single lumen catheter, which is lodged into the anterior naris by a foam collar, inserted to just above the uvula

- Oxygen flows of 2–3 L/min can be used. FiO2 35-40%
- It should not be used when a nasal mucosal tear is suspected because of the risk of surgical emphysema.
- Deep insertion can cause air swallowing and gastric distension
- Must be repositioned every 8 hours to prevent breakdown
- No advantages over nasal cannula.

4. Face mask

Fig 3 - Face Mask

Transparent mask provided with side holes

- Reservoir capacity 100–250 ml
- Different oxygen flow rates result in a highly variable and unpredictable FiO2
- Rebreathing of CO2 can occur with O2 flow rates of less than 2 L O2 l/min or if minute ventilation is very high
- 4 L/min of oxygen flow delivers an FiO2 of about 0.35–0.4 providing there is a normal respiratory pattern
- Flow rates greater than 8L/min do not increase FiO2

Advantage:

- Less expensive (Rs 80/-)
- Can be used in mouth breathers

Disadvantage:

- Uncomfortable
- Require tight seal
- Do not deliver high FiO2
- FiO2 varies with breathing efforts
- Interfere with eating, drinking, communication
- Difficult to keep in position for long
- Chances of rebreathing are high

5. Partial rebreathing mask

- Mask with reservoir bag of capacity 1lit
- Oxygen flows directly into the reservoir bag, which fills during exhalation
- Designed in such a way that it captures exhaled gases from the initial part of

expiration from the dead spaces.

- Useful in situations where supplies are limited
- Deliver an FiO2 between 0.6 and 0.8
- A minimum of 8L/min should enter the mask to remove exhaled CO2 and to refill oxygen reservoir
- Flow rate must be sufficient to keep bag 1/3 to 1/2 inflated at all times

Fig 4 - Partial Rebreathing Mask

Advantage:

- Inspired gas not mixed with room air
- Patient can breath room air through exhalation ports if oxygen supply get interrupted

Disadvantage

- More oxygen flow does not increase FiO2
- Interfere with eating and drinking

6. Non rebreathing mask

Fig 5 - Non Breathing Mask

Provided with one way valves between mask and bag, exhalation ports

- FiO2 of 95% can be achieved with an oxygen flow rates of 10 to 15 L/min
- Ideally NRM should not allow entrainment of air, but because of safety concerns one of the two exhalation ports is not provided with valve
- Higher oxygen supply rates are required
- Desirable in cases where rebreathing of CO2 would be detrimental, for example after head injury
- Best results will be achieved by adequate flow rates such that the reservoir bag empties by no more than a third during inspiration and by best seal possible between the mask and the face

Advantage:

- Highest possible FiO2 without intubation
- Suitable for spontaneously breathing patients with severe hypoxia

Disadvantage :

- Expensive
- Require tight seal, Uncomfortable
- Interfere with eating and drinking
- Not suitable for long term use
- Malfunction can cause CO2 buildup, suffocation

Common high flow devices

1.Venturi mask(AEM)

Fig 6 - Ventury Mask

- Delivers fixed concentration of oxygen
- The size of the constriction determines the final concentration of oxygen for a given gas flow
- As forward flow of inspired gas increases, the lateral pressure adjacent and perpendicular to the vector of flow decreases, resulting in entrainment of gas
- The smaller the orifice is, the greater the negative pressure generated, so the more ambient air entrained, the lower the FiO2
- FiO2 can be 0.24, 0.28, 0.31, 0.35, 0.4 or 0.6

These masks are recommended when a fixed oxygen concentration is desired in patients whose ventilation is dependent on the hypoxic drive

Advantage

- Fine control of FiO2 at fixed flow
- Fixed, reliable, and precise FiO2
- High flow comes from the air, saving the oxygen cost
- Can be used for low FiO2 also
- Helps in deciding whether the oxygen requirement is increasing or decreasing

Disadvantage

- Uncomfortable
- Expensive(400-600)
- Cannot deliver high FiO2
- Interfere with eating and drinking

2. High flow nasal cannula/ HFNO

Fig 7 - HFNC

High-flow nasal oxygen therapy (HFNO) represents an alternative to conventional oxygen therapy. HFNO provides humidified, titrated oxygen therapy matching or even exceeding the patients' inspiratory demand.

It accomplishes a reduction of nasopharyngeal airway resistance leading to improved ventilation and oxygenation through the application of a positive pressure environment.

- Delivers heated and humidified oxygen via special devices (eg, Vapotherm®).
- Rates up to 8 L/min in infants and up to 40 L/min in children and adults. The HFNC overcomes flow limitations of low- and intermediate-flow devices by delivering up to 60 liters per minute of heated, humidified gas via nasal prongs
- In patients with respiratory distress or failure, oxygen by humidified high-flow nasal cannula may be better tolerated than by face mask
- Creates positive nasopharyngeal pressure.
- FiO2 remains relatively constant.
- Because gas is generally warmed to 37°C and completely humidified, mucociliary functions remain good and little discomfort is reported.

High flow of adequately heated and humidified gas is considered to have a number of physiological effects.

1. High flow washes out carbon dioxide in anatomical dead space.

2. Although delivered through an open system, high flow overcomes resistance against expiratory flow and creates positive nasopharyngeal pressure. While the pressure is relatively low compared with closed systems, it is considered adequate to increase lung volume or recruit collapsed alveoli.

3. The difference between the inspiratory flow of patients and delivered flow is small and FIO2 remains relatively constant.

In Covid-19 patients, the current paradigm supports that the acceptable level of hypoxia is up to SpO2 of 92-96%. Several options for oxygen delivery exist as discussed above. These can include a simple nasal cannula, which can provide up to 6 L or approximately 44% FiO2. Further oxygen demand can be met by a non rebreather mask, which can increase flow to 6-10 L while providing 100% FiO2.

Currently, high-flow nasal cannula (HFNC) and noninvasive positive-pressure ventilation (NIPPV) have become standards of care in the ICU for patients with hypoxic respiratory failure and are known to help prevent endotracheal intubation.

Oxygen therapy in home settings:

Due to rising cases of Covid-19, the burden on the healthcare system is increasing with every passing day. Because of the surge in cases, bed and other essential supplies including ventilators, oxygen delivery systems may be insufficient in regional hospitals with a higher number of cases.

According to the recent recommendations, the current COVID-19 inpatient management relies significantly on managing oxygenation status of the patient, hence selected patients could be discharged home if oxygen administration could be addressed in a safe manner, under a well-designed and appropriately implemented regimens. However, the need for diligent and close monitoring of COVID-19 patients who are discharged home is very important due to the possibility of the occurrence of happy hypoxia which can increase the risk of mortality. Also, selection criteria for patients who can be sent home on an oxygen delivering system should be very carefully and diligently curated taking in consideration all the prognostic factors including age, comorbidities, investigation findings etc.

Individual oxygen consumption depends on the duration of the daily administration and the flow rate that allow the arterial oxygen levels to increase sufficiently without causing damaging hypercapnea. For patients treated in the home, the oxygen may be administered in three ways: as gaseous oxygen, via an oxygen concentrator or as liquid oxygen. Each administration type is available in a large dimension form for permanent use as well as in easily portable forms with smaller dimensions.

In consideration with Covid-19, patients usually need smaller portable forms of oxygen delivery systems.

Such as:

- A small cylinder with gaseous oxygen (yield: 0.4m3).
- A small bottle (volume: 0.5 to 1.2 l) with liquid oxygen.
- A portable oxygen concentrator.

While using oxygen delivering systems, the availability of family members or other reliable caretakers who are available to assist with most of the fundamental, non-emergency home care scenarios is of utmost importance. Individuals who are assisting should be educated about staying safe and reducing their own risk of contracting the infection while providing support to the patient. Caretakers as well as patients should be encouraged to take "practice runs" in a simulated setting to learn how to handle the equipment. Caregiver and patient should be well aware about the clinical parameters and their significance in determining the patients health status.

Non-invasive ventilation:

Non-invasive ventilation (NIV) is a method of respiratory support, in which a mask is used as the main interface, which can be easily applied and easily disconnected from the patient's respiratory tract.

The harmful effects of the treatment of Respiratory Distress Syndrome (RDS) with invasive ventilation have led to a deeper study of non-invasive ventilation methods (NIV).

NIV assists breathing by supplying a mixture of air and oxygen using positive pressure to help the patient to take deeper breaths, so improving oxygenation without an airway adjunct, via a tight mask or a hood. The patient must be conscious, able to initiate their own breaths and to maintain their own airway.

- **CPAP (continuous positive airways pressure)**

Fig 8 - CPAP

- A Continuous Positive Airway Pressure (CPAP) Ventilator provides a positive pressure which is held constant throughout the respiratory cycle.
- The patient has to initiate each breath.
- CPAP improves the lung mechanics by recruiting collapsed alveoli, keeping them open and thus improving gas exchange, improving lung compliance and reducing the work of breathing. While it opens up the alveoli there is a redistribution of the alveolar fluid, relieving pulmonary edema. This also improves the ventilation over perfusion matching of the lungs.
- Also, with CPAP, there is increased intrathoracic pressure that decreases the venous return to the heart, i.e. decreased preload.
- CPAP is mainly used in patients whose primary problem is hypoxemia.
- CPAP is used frequently in patients with cardiogenic pulmonary edema (Congestive Heart Failure) and for Obstructive Sleep Apnea / Hypopnea.
- Pressures of 5 to 10 cm of H20 are commonly used, and pressures above 1 5 are rarely used.-

- **BiPAP (bilevel positive airways pressure)**

Fig 10 - BiPAP

- Bi-level Positive Airway Pressure Bi-level Positive Airway Pressure (BiPAP) is a method of NIPPV where the patient's spontaneous ventilation is assisted at a "bilevel".
- BiPAP ventilators provide positive airway pressure that cycles between high positive pressure and low positive pressure.
- The positive airway pressure increases during inspiration and a lower positive expiratory pressure provides the physiological positive end-expiratory pressure (PEEP).

- BiPAP machines respond to the patient's respiratory efforts and cycle between a higher flow during inspiration and a lower flow during expiration.
- The average starting range for inspiratory positive airway pressure (IPAP) is 8 to 10 cm H20 whereas expiratory positive airway pressure (EPAP) is 3 to 5 cm H20.
- BiPAP is used for patients whose primary problem is hypoventilation.
- It is commonly used in patients with COPD, in immuno-compromised patients and postextubation.

- **Invasive ventilation/Mechanical Ventilator**
-

Fig 11 - Mechanical Ventilator

- Fully controlled oxygen delivery up to 100%
- A ventilation bag or machine is attached to an artificial airway to ventilate lungs.
- Used in intensive care units
- Compressor based ventilator preferred in covid

Modes of Ventilation

1. Controlled Ventilation

- Vent initiates all breaths at a pre-set rate and tidal volume
- Vent will block any spontaneous breaths
- Used mainly in the OR for paralyzed and sedated patients.

2.Assist Control (A/C)

- Vent will allow a patient to initiate a breath and then vent will deliver a pre-set tidal volume

- Machine set at a minimum rate so apnea will not occur if the patient does not initiate a breath

3.Synchronized Intermittent Ventilation (SIMV)

- Similar to A/C, but patients can take own breaths with their own TV between mechanically assisted breaths
- Can be used as a primary mode or a weaning mode
- May lead to a low respiratory rate in a patient who does not initiate breaths if set rate is low

4.Pressure Support Ventilation (PSV)

- Also called "spontaneous mode"
- Pt initiates breath & vent delivers a pre-set inspiratory pressure to help overcome airway resistance and keeps airways open
- Patient controls the rate, tidal volume, and minute ventilation
- Tidal volume is variable
- Can be used in conjunction with SIMV or CPAP settings

5.Continuous Positive Airway Pressure (CPAP)
Positive airway pressure provided during both inspiration and expiration

- Vent provides O2 and alarms, but no respirations
- Improves gas exchange and oxygenation in patients able to breathe on their own
- Can also be used non-invasively via a face or nasal mask for patients with sleep apnea

6.Airway Pressure ReleaseVentilation (APRV)

- Differs from conventional vent
- Elevation of airway pressures with brief intermittent releases of airway pressure
- Facilitates oxygenation and CO2 clearance
- May be an improved way to treat ALI/ ARDS

Closed loop v/s open loop ventilators:

The closed-loop ventilators can be called as "complete automatic control" of mechanical ventilation. For example, pressure support ventilation (PSV) uses closed-loop control. The clinician has to set a target pressure (the pressure support setting) and flow is automatically adjusted by the ventilator to maintain that pressure throughout inspiration.

In the open loop systems, the operator or physician has to set the parameters. Open loop ventilators, then deliver the preset parameters to the patient. Open loop system can not adjust the parameters depending upon the input or output variable.

Stethoscope:

Fig 12 - Stethoscope

Stethoscopes are used regularly by medical personnel to listen to acoustic signals picked from the internal parts of the human body during diagnosis and treatment of patients.

A typical stethoscope is made up of three components: the head-piece, chest-piece, and a connecting cable that serves as a communication link between the two main components.

The novel wireless stethoscope design consists of two modules: an integrated chest-piece that serves as the transmitting system and integrated headpiece that serves as a receiver system. The chest-piece system consists of the data acquisition interface that is integrated with the wireless module whereas the head-piece system consists of an integrated wireless receiver unit and a microcontroller. The movement of the data from the chest-piece circuit to the head-piece was achieved via Bluetooth wireless connection.

A full two-piece wireless electronic stethoscope can make possible the easy movement of the device users around patients during auscultation, and also minimize the spread of infections.

UV sterilizer

Fig 13 - UV Sterilizer

Ultraviolet (UV) light is a form of electromagnetic radiation with more energy than visible light, but less energy than x-rays. Although there is no current consensus on the amount of UV radiation required to inactivate SARS-CoV-2, the single-stranded RNA (ssRNA) virus that causes COVID-19, the UV dose required to inactivate 90% of ssRNA viruses is an estimated 1.32−3.20 mJ cm.

A major advantage of UV treatment is that it is considered safer and more reliable for disinfection of water than chemical alternatives, while the level of disinfection is much higher. UV treatment systems are also extremely cost efficient and require less space than regular disinfection systems.

UV sterilizer box, available in India consists of following specifications:

- Capacity- 45 Litres
- Application- 360 Degree Disinfection
- Specification:- 3 OSRAM UVC Germicidal Lamps (2X8W and 1X11W), having a wavelength of 254nm.
- Features:- 1) Digital Timer 2) Auto cut off lights when door opens

Corona Guard

This device is manufactured and marketed in India by Eureka Forbes under the brand name FORBES CORONAGUARD (Powered by SHYCOCAN). It provides real-time protection from covid-19 by using novel electron cloud technology.

Corona virus consists of spike protein covering the outer surface. The Spike Protein seeks the host cell receptors thereby infecting people by multiplying thereafter. The Corona guard Hyper-Charged canon emits trillions(10-100 trillion per second) of photons, forming an Electron Cloud that covers the entire space. The negatively charged electrons neutralize the positively charged S-proteins in the air and on surfaces, eliminating the bridge between the virus and the human cells.

The CORONAGUARD does not use any chemicals nor does it produce ozone, or ionize the air to produce reactive oxygen species, oxides of nitrogen or other harmful compounds; hence, the device can be safely deployed in all environments inhabited by people, be it very large or small enclosed spaces. It is useful in high-risk as well as essential environments.

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38 Personal Protective Equipment

Even though scientists around the globe are working meticulously on the treatment of Covid-19, there is no definitive cure of Covid-19, as of now. Hence, infection prevention is the only definitive way to be safe from the hazardous effects this virus has on the body. Hence in this chapter, we will be focusing on the various instruments used in medical as well as non-medical set up to prevent frontline corona warriors from getting infected.

Personal Protective Equipment (PPE)

Personal Protective Equipment (PPEs) are protective gears that are designed to safeguard the health of workers by minimizing the exposure to a biological agent(virus).

Components of PPE

PPE usually consists of goggles, face-shield, mask, gloves, coverall/gowns (with or without aprons), head cover and shoe cover.

1.Face shield and goggles

Fig 1 - Goggles

Droplets generated by cough, sneeze of an infected person or during aerosol generating procedures carried out in a clinical setting, there are high chances of the contamination of mucous membranes of the eyes, nose and mouth. Unknowingly touching the face including eyes/nose/mouth with a dirty hand also increases the risk of infection. Hence protection of the mucous membranes of the eyes/nose/mouth by using face shields/ goggles is an integral part of standard and contact precautions.

The frame of goggles should be flexible in order to provide a good seal with the skin around the eyes, fully covering the eyes and the surrounding areas. It should also have a space for accommodating prescription glasses.

Polycarbonate is the material of choice for many helmet-style face shields because of its optical clarity and impact resistance; however, when it has been used for medical purposes to prevent contraction from any biomedical agent polyester is widely used. Polyester is as thin as it can be cut by the scissors; however, thick enough to hold it's shape.

For the headband, a simple foam band that rides on the forehead and holds the lens plate, coupled with an adjustable length of 1 inch can be used. Wide elastic band can also be used. So that the product can be easily disposable and inexpensive.

Specifications for face shield:

- Made of clear plastic and provides good visibility to both the wearer and the patient
- Adjustable band to attach firmly around the head and fit snugly against the forehead
- Fog resistant (preferable)
- Completely covers the sides and length of the face
- May be re-usable (made of material which can be cleaned and disinfected) or disposable
- Quality compliant with the below standards, or equivalent:

a. EU standard directive 86/686/EEC, EN 166/2002
b. ANSI/SEA Z87.1-2010

Specifications for goggles:

With transparent glasses, zero power, wellfitting, covered from all sides with

elastic band/or adjustable holder.

- Good seal with the skin of the face
- Flexible frame to easily fit allface contours without too much pressure
- Covers the eyes and the surrounding areas and accommodates for prescription glasses
- Fog and scratch resistant
- Adjustable band to secure firmly so as not to become loose during clinical activity
- Indirect venting to reduce fogging
- May be re-usable (provided appropriate arrangements for decontamination are in place) or disposable
- Quality compliant with the below standards, or equivalent:

a. EU standard directive 86/686/EEC, EN 166/2002
b. ANSI/SEA Z87.1-2010

2.Masks

Fig 2 - N95

Coronaviruses mainly target the upper and lower respiratory tracts. Hence protecting the airway from the particulate matter generated by droplets / aerosols is an important way of preventing the infection. Infection can also occur through mucous membranes of the mouth and nose by infective droplets or by touching the face with a contaminated hand. Hence the droplet precautions/airborne precautions using masks are crucial while dealing with a suspect or confirmed case of COVID-19 or during performing aerosol generating procedures.

Masks are of different types.

The type of mask to be used depends upon the risk profile of a work, particular

person is doing.

There are two types of masks which are recommended for various categories of personnel working in hospital or community settings, depending upon the work environment:

1. Triple layer medical mask
2. N-95 Respirator mask

-Triple layer medical mask

A triple layer medical mask is a disposable mask, which is fluid-resistant, provides protection from droplets of infectious material emitted during coughing/sneezing/talking.

It is important to have three layers to the mask because an inner layer absorbs, a middle layer acts as a filter, and an outer layer should be made from a non-absorbent material like polyester. Those layers in that order can provide a mechanistic barrier.

Specifications:

- Three layered medical mask of non-woven material with nose piece, having filter efficiency of 99% for 3 micron particle size.

a. ISI specifications or equivalent

All medical personnel including nursing and paramedical staff in the screening and isolation area can wear disposable triple layer masks while interacting with patients. Also, the driver of the ambulance, paramedic, security personnel can use the triple layer masks. However, if the staff is involved in any aerosol generating procedures like suction, intubation, nebulization, etc. they must use N95 Respirator. If the medical personnel need to collect clinical samples from patients then they would also use N95 Respirators.

Triple layer masks should not be reused.

The correct procedure of wearing triple layer surgical mask :

- Unfold the pleats; make sure that they are facing down.
- Place over nose, mouth and chin.
- Fit flexible nose piece over nose bridge.
- Secure with tie strings (upper string to be tied on top of head above the ears

lower string at the back of the neck.)
- Ensure there are no gaps on either side of the mask, adjust to fit.
- Do not let the mask hang from the neck.
- Change the mask after six hours or as soon as they become wet.
- Disposable masks are never to be reused and should be disposed of. While removing the mask great care must be taken not to touch the potentially infected outer surface of the mask
- To remove the mask first untie the string below and then the string above and handle the mask using the upper strings.

Disposal of used masks

- Used masks should be considered as potentially infectious medical waste.
- In the hospital setting it should be disposed off in the identified infectious waste disposal bag/container.
- In community settings where medical waste management protocol cannot be practiced, it may be disposed off either by burning or deep burial.

N-95 Respirator mask

An N-95 respirator mask is a respiratory protective device with high filtration efficiency against airborne particles. These masks are made in such a way that they will provide a very close facial fit. Such masks should have high fluid resistance, good breathability (preferably with an expiratory valve), clearly identifiable internal and external faces, duckbill/cup-shaped structured design that does not collapse against the mouth. If correctly worn, the filtration capacity of these masks exceeds those of triple layer medical masks. Since these provide a much tighter air seal than triple layer medical masks, they provide protection from inhaling airborne particles.

Medical and nursing staff involved in critical care in ICUs, all personnel working in laboratories and handling clinical samples should wear N-95 Respirator masks.

Respirator masks are divided into 3 categories according to The EN 149 named as FFP1, FF2, FFP3. FFP is a short form for filtering facepiece particles.

FFP1

- Protection from non-toxic and non-fibrogenic kinds of dust
- Inhaling may result in development of health conditions; can also irritate the respiratory system and cause unpleasant odors

- Filters at least 80% of airborne particles
- Total leakage may amount to a maximum of 25 %

FFP2

- Protection from firm and fluid deleterious kinds of dust, smoke, and aerosols
- Particles may be fibrogenic – which means they irritate the respiratory system in the short term and can result in reduction of elasticity of pulmonary tissue in the long run
- Filters at least 94% of airborne particles
- Total leakage may amount to a maximum of 11%

FFP3

- Protection from poisonous and deleterious kinds of dust, smoke, and aerosols
- When working with oncogenic or radioactive substances or pathogens such as viruses, bacteria and fungal spores FFP3-class respirator masks are recommended
- Filters at least 99% of airborne particles
- Total leakage may amount to a maximum of 5%

FFP2 is considered as the minimum protection needed, FFP3 being the preferred solution for the health care workers involved in the ICU, laboratories or in the handling of the clinical samples.

FFP2 / FFP3 masks are typically non reusable.

Specifications:

- Shape that will not collapse easily
- High filtration efficiency
- Good breathability
- Quality compliant with standards for medical N95 respirator:

a. NIOSH N95, EN 149FFP2, or equivalent

- **Fluid resistance:**

minimum 80 mmHg pressure based on ASTM F1862, ISO 22609, or equivalent

- **Quality compliant with standards for particulate respirator that can be**

worn with full-face shield

Avoid using the mask with an expiration valve. These are one-way valves, with the filter functional only in one direction. During inspiration, the air you inhale is filtered. But, as you exhale, the mixture of carbon dioxide, oxygen, water vapor and, possibly COVID-19 viral particles releases unfiltered. The San Francisco Department of Public Health actually tweeted a warning that these masks may actually propel your germs further.

3.Gloves

Fig 3 - Gloves

Person may get exposed to the virus when he touches an object/surface contaminated by COVID-19 infected person, and then touches his own eyes, nose, or mouth. This is thought to be one mode of transmission, so care should be exercised while handling objects/surface potentially contaminated by suspect/confirmed cases of COVID-19.

Types of gloves:

1.Nitrile gloves

2.Latex gloves

Nitrile gloves are preferred over latex gloves because they resist chemicals, including certain disinfectants such as chlorine. The rate of allergies to latex and contact allergic dermatitis among health workers is a common issue. However, if nitrile gloves are not available, latex gloves can be used. Non Powdered gloves are preferred to powdered gloves.

Specifications:

- Nitrile

- Non-sterile
- Powder free
- Outer gloves preferably reachmid-forearm (minimum 280 mm total length)
- Different sizes (6.5 &7)
- Quality compliant with the below standards, or equivalent:

a. EU standard directive 93/42/EECClassI,EN455
b. EU standard directive 89/686/EEC Category Ill, EN 374
c. ANSI/SEA 105-2011 d. ASTM D6319-10

4.Coverall/Gowns

Fig 4 - Coveralls

Coveralls are designed to protect the torso of healthcare providers from exposure to viruses. Coveralls typically provide 360-degree protection because they are designed to cover the whole body, including back and lower legs and head and feet as well.

The design of medical gowns do not provide continuous whole-body protection (e.g., possible openings in the back, coverage to the mid-calf only).

By using appropriate protective clothing, it is possible to create a barrier to avoid or reduce contact and droplet exposure, thus protecting healthcare workers who are working in close proximity (within 1 meter) of suspect/confirmed COVID-19 cases or their secretions.

As there is a lack of comparative evidence to show whether one is more effective

than the other, coveralls and gowns are equally acceptable. Gowns are considerably easier to put on and to remove after the use. An apron can also be worn over the gown for the entire time the health worker is in the treatment area. Coveralls are recommended in high risk covid areas such as triage, hospital wards, icu etc.

The fabric material for manufacturing PPE coverall are synthetic fibres, such as, polypropylene (PP), polyester (PET), polyethylene (PE), and nylon. The fabric type is mainly non-woven, which is single-use.

Usually the stitched seam is sealed by overlaying tape. This process is called "seam sealing" and requires special machinery called "hot air seam sealing machine". The hot air seam sealing machine uses adhesive tape as consumable. For a medical PPE, usually a 2 layer seam sealing tape is used, which is designed to seal the seams on light to medium weight, PP and PE fabrics.

Specifications:

- Single use

Impermeable to blood and body fluids

- Avoid culturally unacceptable colors e.g. black
- Light colors are preferable to better detect possible contamination
- Thumb/finger loops to anchor sleeves in place
- Quality compliant with following standard

a. Meets or exceedsISO 16603 class 3 exposure pressure, or equivalent

5. Shoe covers

Fig 5 - Shoe Covers

Shoe covers should be made up of impermeable fabric to be used over shoes to facilitate personal protection and decontamination.

The most common material used to make shoe covers is blue Polypropylene (PP) fabric.

Specifications:

- Made up of the same fabric as of coverall
- Should cover the entire shoe and reach above ankles

6.Head covers

Fig 6 - Head Cover

Coveralls usually cover the head. Those using gowns, should use a head cover that covers the head and neck while providing clinical care for patients. Hair and hair extensions should fit inside the head cover. The head covers are made from high quality non woven fabric and are single use purpose.

Please note that PPEs are not alternative to basic preventive public health measures such as hand hygiene, respiratory etiquettes which must be followed at all times.

Always (if possible) maintain a distance of at least 1 meter from contacts/suspect/confirmed COVID-19 cases

Always follow the laid down protocol for disposing off PPEs as detailed in infection prevention and control guidelines.

Donning and doffing of PPE:

Separate donning and doffing areas:

- Ensure that areas for donning and doffing are designated as separate from the patient care area and one-way flow from the donning area to the patient care area to the doffing area should be maintained.
- Confirm that the doffing area is large enough to allow freedom of movement for safe doffing as well as have a space for waste material collection, a new glove supply, and ABHR used during the doffing process.

Donning

PPE must be donned correctly in proper order before entry into the patient care area; PPE should not be later modified while in the patient care area. The donning activities must be directly observed by a trained observer. During the patient care, PPE must remain in place and be worn correctly for the duration of work in potentially contaminated areas. PPE should not be adjusted during patient care.

Healthcare workers should perform frequent disinfection of gloved hands using an ABHR, particularly after contact with body fluids.

If during patient care any breach in PPE occurs (e.g., a tear develops in an outer glove, a needlestick occurs, a glove separates from the sleeve), the healthcare worker must move immediately to the doffing area to assess the exposure.

Precautions to be taken before donning:

- HCW should have a meal, drink water and should washroom before entering the donning area
- Remove all accessories including jewellery, watches etc
- Perform hand hygiene with soap and water
- Gather all the PPE items that you will be needing.
- Use the designated area only while donning
- Inspect the PPE for any damage or breach
- Don PPE before patient contact
- Avoid touching any surfaces or objects other that PPE items while donning
- Perform hand hygiene prior to each step.

Steps to follow while donning:

1. Perform hand hygiene.
2. Put on shoe covers (if applicable).
3. Perform hand hygiene
4. Put on a gown.

Fully cover your torso from your neck to knees and your arms to the end of your wrists, then tie at the back. The gown should be large enough to allow unrestricted movement without gaping. Fasten at the back of the neck and waist.

5. Perform hand hygiene
6. Put on a surgical mask or P2/N5 respirator.

Secure the ties or elastic bands at the middle of the head and neck.

Fit flexible band to the nose bridge.

Fit mask snug to face and below the chin.

Fit-check respirator according to manufacturer instructions.

7. Perform hand hygiene
8. Put on protective eyewear or face shield.

Place over eyes/face and adjust to fit.

9. Perform hand hygiene
10. Put on gloves
11. Extend the gloves to cover the wrist of the gown.

If at any point your gloves become contaminated, you must dispose of them, perform hand hygiene and then replace them with new gloves.

Doffing

Removing used PPE is a high-risk process that requires a structured procedure, a trained observer, a doffing assistant when applicable or needed, and a designated clean area for removal to ensure protection.

PPE must be removed slowly and deliberately in the correct sequence to reduce the possibility of self-contamination or other exposure to Ebola.

A stepwise process should be developed and used during training and patient care.

Steps to be followed while doffing:

Perform hand hygiene immediately after each step of doffing (Queensland DoH 2020).

Your gloves and gown should be removed before exiting the patient area.

Take help of the observer, to examine for any breach or tear in the PPE.

Check the PPE for any gross contamination which could be disinfected using alcohol based wipes.

1. Sit on a chair. Remove the shoe covers by slowly pulling the outer surface starting from the top. Do not croothe legs while sitting.

2. Perform hand hygiene.

3. Remove gloves.
   Grab the glove at the anatomical snuff box or at the wrist and pinch it to pull it inside out, hold this glove like a ball in the other hand. Then slide the thumb inside the other glove, to remove it inside out balling around the previous glove, making it a single bag.
   Perform hand hygiene.
   Discard gloves in a waste container.

4. Perform the hand hygiene.

5. Remove goggles/face shield.
   Hold the strap, lean over and remove it without letting it touch your face.
   Remove from the back of the head by lifting headband or ear pieces.

   If reusable, place in the designated reprocessing receptacle. If not, discard in the waste container.

6. Perform hand hygiene.

7. Remove the gown/ coverall.
   Unfasten the ties or velcro strap, ensuring the sleeves don't make contact with your body.
   Pull the gown away from the neck and shoulders, touching the inside only.
   Turn the gown inside out.
   Fold or roll the gown into a bundle and discard in the waste container.

8. Perform hand hygiene.

9. Carefully remove the pair of second gloves as previously described.

10. Perform hand hygiene.

11. Wear a new pair of gloves before removing the mask.

12. Remove mask/respirator.
    Grasp the bottom ties/elastics, then the top ones, and remove without touching the front of the mask by leaning or stooping forward.
    Discard in the waste container.

13. Immediately perform hand hygiene.

14. Use alcohol wipes to clean the outer surface of the shoes by sitting in a clean chair.

15. Perform hand hygiene.

16. Now, remove the last pair of gloves.

17. Perform hand hygiene.

18. Wipe your shoes on sodium hypochlorite soaked doormat at the exit.

Summary:
Always perform hand hygiene before and after wearing PPE:

i. PPE should be available where and when indicated according to risk in the correct size
ii. Always put PPE on before contact with the patient
iii. Remove PPE immediately after completing the task and/or leaving the patient care area
iv. Never reuse disposable PPE
v. PPE kits to be donned and doffed under observation in the specified area only.
vi. Change PPE immediately if it becomes soiled/ contaminated or damaged
vii. PPE should not be adjusted or touched during patient care
viii. Never touch your face while wearing PPE
ix. If there is concern and/or breach of these practices leave the patient care area when safe to do so properly remove and change the PPE. (INFORM the MEDICAL OFFICER about Breach of PPE/ Exposure, for Post exposure measures Immediately)
x. Always remove PPEs remove carefully to avoid self-contamination
xi. From dirtiest to cleanest areas
xii. Always enter donned with full compliant PPE kit in the demarcated
xiii. Do not reuse PPE in the ISOLATION, Triage area.

References:

1. World Health Organization. Rational use of personal protective equipment (PPE) for coronavirus disease (COVID-19): interim guidance, 19 March 2020. World Health Organization; 2020.

2. Honda H, Iwata K. Personal protective equipment and improving compliance among healthcare workers in high-risk settings. Current opinion in infectious diseases. 2016 Aug 1;29(4):400-6.

3. Doll M, Feldman M, Hartigan S, Sanogo K, Stevens M, McReynolds M, Masroor N, Cooper K, Bearman G. Acceptability and necessity of training for optimal personal protective equipment use. infection control & hospital epidemiology. 2017 Feb;38(2):226-9.

4. https://www.cdc.gov/vhf/ebola/healthcare-us/ppe/guidance.html

39 Ongoing Clinical Trials in India

1.	CTRI/2020/04/024413	Knowledge, attitude and fear of COVID-19 in Bangladesh	Bangladesh health Professions Institute,N/A
2.	CTRI/2020/05/025319	Trial of antihypertensive losartan for additional benefit in treating COVID 19 infection.	Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow,UTTAR PRADESH
3.	CTRI/2020/04/024482	A pan-india non-interventional virtual registry evaluating the prophylactic efficacy of different regimens against SARS-CoV2 infection (COVID-2019) in asymptomatic health care workers	Zifo RnD Solutions,TAMIL NADU
4.	CTRI/2020/04/024806	Imatinib in COVID-19 infection	All India Institute of Medical Sciences,DELHI
5.	CTRI/2020/04/024882	A study to assess the effectiveness of Ayurvedic formulation in addition to standard of care in COVID-19 positive patients in a tertiary hospital.	Medanta Institute of Education and Research,HARYANA
6.	CTRI/2020/04/024731	Study to Evaluate Preventive Effect of Ayurveda and Homeopathy Treatment in COVID 19	Parul Ayurved Hospital,GUJARAT

7.	CTRI/2020/04/024729	Topical Chloroquine Nasal Drops in Early Stage Covid 19- Impact on Viral load and cure rates	National Cancer Institute,HARYANA
8.	CTRI/2020/04/024846	A Clinical Trial of Mycobacterium w in Critically Ill COVID 19 Patients	All India Institute of Medical Science, Raipur,CHHATTISGARH All India Institute of Medical Sciences, Bhopal,MADHYA PRADESH All lndia Institute of
			Medical Science, Delhi,DELHI Post Graduate Institute of Medical Education and Research,CHANDIGARH Sir Sundar Lal Hospital Institute of Medical Sciences Banaras Hindu University,UTTAR PRADESH
9.	CTRI/2020/05/025242	Hydroxychloroquine of pharmacokinetics in healthcare workers	Dept of Clinical Pharmacology,MAHARASHTRA
10.	CTRI/2020/04/024833	BCG-Denmark versus no-BCG for COVID 19 prevention	Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry,PONDICHERRY
11.	CTRI/2020/04/024747	EFFECTIVENESS TO MANAGE COVID 19 PANDEMIC BY TEACHING VENTILATORY MANAGEMENT TO NON-ANAESTHESIOLOGY RESIDENTS	SIMULATION LAB, GSL MEDICAL COLLEGE,ANDHRA PRADESH
12.	CTRI/2020/08/027043	Mesenchymal Stem Cell Therapy For Covid 19	Seven Hills Hospital,MAHARASHTRA

13.	CTRI/2020/05/025271	Clinical Trial of Mycobacterium w in COVID-19 Positive Patients, Hospitalized But Not Critically Ill	All lndia Institute of Medical Science, Delhi,DELHI AII India Institute of Medical Science, Raipur,CHHATTISGARH All India Institute of Medical Sciences, Bhopal,MADHYA PRADESH Grant Government Medical College & Sir J.J. Group of Hospitals,MAHARASHTRA Post Graduate Institute of Medical Education and Research,CHANDIGARH
14.	CTRI/2020/04/024858	"To study the effectiveness of Ivermectin with standard of care treatment versus standard of care treatment for COVID 19 cases. A Pilot Study	Max Super Speciality hospital, Saket (A unit of Devki Devi Foundation),DELHI
15.	CTRI/2020/05/025183	Questionnaire based study of drugs taken by healthcare workers to prevent COVID 19	AIIMS Bhopal,MADHYA PRADESH AIIMS Delhi,DELHI BJMC Ahmedabad,GUJARAT CMC Ludhiana,PUNJAB CMC Vellore,TAMIL NADU Dayanand Medical College and Hospital Ludhiana,PUNJAB GMC Baroda,GUJARAT GSMC KEM,MAHARASHTRA IGIMS Patna,BIHAR IPGMER Kolkata,WEST BENGAL

			JIPMER Puducherry,PONDICHERRY PGIMER Chandigarh,CHANDIGARH School of Tropical Medicine Kolkata,WEST BENGAL St. Johns Medical college Bangalore.,KARNATAKA Vardhaman Medical College Delhi,DELHI
16.	CTRI/2020/04/024947	Clinical trial on effects of homeopathic medicine made from cadamba on COVID-19	homoeo clinic ,MAHARASHTRA
17.	CTRI/2020/05/025010	Hydroxychloroquine prophylaxis in Covid 19 infection	AIIMS Bhubaneswar,ORISSA AIIMS Jodhpur,RAJASTHAN AIIMS PATNA,BIHAR Apollo Hospitals,TAMIL NADU Maulana Azad Medical college and associated Lok Nayak Hospita,DELHI Sir Ganga Ram Hospital,DELHI
18.	CTRI/2020/05/025049	A CLINICAL TRIAL TO STUDY THE EFFICACY OF HOMOEOPATHIC MEDICINE IN PREVENTION AND CURE OF CORONA VIRUS	SAI NIDAN HOMOEOPATHY CLINIC,CHHATTISGARH

		DISEASE 19	
19.	CTRI/2020/05/025331	Home based prehabilitation via telemedicine in lung cancer patients during COVID 19	Dr BRAIRCH, AIIMS,DELHI
20.	CTRI/2020/05/024989	Mechanism of Covid 19 infection in Humans	AIG Hospitals,TELANGANA
21.	CTRI/2020/05/024984	How has the spread of COVID 19 disease affected the teaching and training of postgraduate students who are studying anaesthesiology	Sanjay Gandhi Post Graduate Institute of Medical Sciences,UTTAR PRADESH
22.	CTRI/2020/05/025068	Can a medicine help in curing viral infection	Christian Medical College Vellore,TAMIL NADU
23.	CTRI/2020/05/024986	HOMOEOPATHY IN PREVENTION OF COVID-19	Hot spots of Covid -19 in Delhi,DELHI
24.	CTRI/2020/05/025369	A study on treatment of COVID-19 patients with study drug along with standard of care	Apollo Hospitals-Hyderabad,TELANGANA Apollo Speciality Hospitals-Vanagaram,TAMIL NADU Artemis Hospital,HARYANA B J Medical College and S G H B J Medical College and Sassoon General Hospital,MAHARASHTRA Fortis Hospitals Limited Mulund,MAHARASHTRA Fortis Memorial Research Institute,HARYANA Indraprastha Apollo Hospitals,DELHI Medanta- The Medicity,HARYANA

			Medeor Hospital,HARYANA Nayati Hospital ,UTTAR PRADESH P. D. Hinduja Hospital and Medical Research Centre,MAHARASHTRA Pt. B. D. Sharma Post Graduate Institute of Medical Sciences,HARYANA Sanjay Gandhi Post Graduate Institute of Medical Sciences,UTTAR PRADESH
25.	CTRI/2020/05/025114	A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With Mild to Moderate COVID-19.	AIIMS,CHHATTISGARH Breach Candy Hospital Trust,MAHARASHTRA Dr. Balabhai Nanavati Hospital,MAHARASHTRA Fortis Hospital Limited,MAHARASHTRA GMERS Medical college & Hospital,GUJARAT Government medical college and hospital,MAHARASHTRA Government medical college and hospital ,MAHARASHTRA

			HCG Hospital,GUJARAT Kasturba Hospital for Infectious Disease ,MAHARASHTRA Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute,MAHARASHTRA Max Smart Super Speciality Hospital ,DELHI SSG Hospital & Medical College Baroda,GUJARAT
26.	CTRI/2020/05/025069	Ayurvedic Interventions in prevention of COVID-19 infection-A survey study	Containment zone of COVID 19 at Delhi,DELHI Containment zone of COVID 19 at Delhi,DELHI Containment zone of COVID 19 at Delhi,DELHI
27.	CTRI/2020/05/025166	Study of ASHWAGANDHA TABLET on healthy individuals to prevent covid 19	Regional Ayurveda research institute for skin disorders , new rajeev nagar Vijayawada ,ANDHRA PRADESH
28.	CTRI/2020/05/025088	Study of GUDUCHI TABLET on healthy individuals to prevent covid 19.	Regional Ayurveda research institute Vijayawada,ANDHRA PRADESH
29.	CTRI/2020/05/025487	Development of Smell based test for identifying COVID-19 infection.	Department of Endocrinology, PGIMER, Chandigarh,CHANDIGARH
30.	CTRI/2020/07/026698	COVID 19 and changes in the heart	Jayadeva Institute of Cardiovascular Sciences ,KARNATAKA
31.	CTRI/2020/05/025092	Outcomes of viral infection in	Christian Medical College

		hematology patients	Vellore,TAMIL NADU
32.	CTRI/2020/05/025091	Knowledge status of public about COVID 19 disease prevention and control in Tamil Nadu	Siddha Central Research Institute,TAMIL NADU
33.	CTRI/2020/05/025238	Emotional Impact of Isolation during COVID 19 among college students and staff	Kasturba Medical College ,KARNATAKA
34.	CTRI/2020/06/026198	Conscious posture therapy and covid 19 hypoxemia	nehru hospital extension,CHANDIGARH
35.	CTRI/2020/05/025291	Corona virus in tears	Maulana Azad Medical College,DELHI
36.	CTRI/2020/05/025213	Ayurveda formulation for COVID-19 prevention	Regional Ayurveda research institute for Nutritional Disorders,HIMACHAL PRADESH
37.	CTRI/2020/05/025328	Study to Assess the Safety and Efficacy of Convalescent Plasma on outcome of COVID-19 Associated Complications	Apollo Gleneagles Hospitals,WEST BENGAL Apollo Hospitals,TELANGANA Apollo Hospitals,MAHARASHTRA Apollo Specialty Hospitals,TAMIL NADU Indraprastha Apollo Hospitals ,DELHI
38.	CTRI/2020/05/025482	Effect of nutritional supplement made from Haldi and Black Pepper to prevent and treat active corona virus infection	GMC BARAMATI AND RURAL HOSPITAL,MAHARASHTRA
39.	CTRI/2020/05/025205	Arsenicum album – 30 as prophylactic for Covid-19	Hot spots of Covid -19 in Chennai,TAMIL NADU Hot spots of Covid -19 in

			Delhi,DELHI Hot spots of Covid -19 in Gudivada and Vijaywada,ANDHRA PRADESH Hot spots of Covid -19 in Hyderabad,TELANGANA Hot spots of Covid -19 in Jaipur,RAJASTHAN Hot spots of Covid -19 in Kolkata,WEST BENGAL Hot spots of Covid -19 in Kottayam,KERALA Hot spots of Covid -19 in Lucknow,UTTAR PRADESH Hot spots of Covid -19 in Mumbai,MAHARASHTRA Hot spots of Covid -19 in Noida,UTTAR PRADESH Hot spots of Covid -19 in Surat,GUJARAT
40.	CTRI/2020/05/025214	To observe the effect of Ayurvedic medicine for the treatment of COVID-19	Shri Dhanwantry Ayurvedic College and Hospital,CHANDIGARH
41.	CTRI/2020/05/025299	Convalescent Plasma treatment trial in COVID 19 patients	Wockhardt Hospital Pvt Ltd,MAHARASHTRA
42.	CTRI/2020/05/025221	Create registry of Childhood Cancer patients in India with COVID 19 to provide guidelines for prevention and treatment	Max Super Speciality Hospital,DELHI

43.	CTRI/2020/05/025216	HCQ POCKET ECG Ambulatory Telemetry Study	All India Institute of Medical science Rishikesh ,UTTARANCHAL
44.	CTRI/2020/06/025844	Pre-Identified Homoeopathic Medicines In Asymptomatic Covid -19 Individuals Receiving Standard Treatment Protocol	Government Homoeopathic Medical College and Hospital,MADHYA PRADESH
45.	CTRI/2020/05/025298	Siddha Intervention Population Study.	siddha central research institute,TAMIL NADU
46.	CTRI/2020/08/027094	Role of Digital communication in COVID 19 isolation facilities an observation study	National Cancer Institute, Jhajjar,HARYANA
47.	CTRI/2020/05/025215	Effectiveness of Siddha medicine, Kabasura kudineer and vitamin c-zinc supplementation in the management of Mild COVID 19 patients.	Government Stanley Medical College,TAMIL NADU
48.	CTRI/2020/06/026151	Ayurveda and Yoga trial for preventing COVID 19 among healthcare workers	All India Institute of Medical Sciences, New Delhi,DELHI
49.	CTRI/2020/06/026147	Ayurveda and Yoga trial for preventing COVID 19 among quarantined individuals exposed to COVID 19 patients	All India Institute of Medical Sciences, New Delhi,DELHI
50.	CTRI/2020/05/025272	A study to assess the efficacy of Homoeopathic medicine in the prevention of Covid-19	District Medical Office (Homoeo), Palakkad,KERALA
51.	CTRI/2020/06/025795	Effects of Lockdown during Corona Pandemic on children with Neurodevelopmental Disorders-A Questionnaire based survey	Army Hospital Research and Referral,DELHI
52.	CTRI/2020/05/025333	Study to assess efficacy of Ivermectin as prophylaxis of COVID -19	R D Gardi Medical College, Ujjain ,MADHYA PRADESH

53.	CTRI/2020/05/025293	Difficulties faced by pregnant women during the Covid 19 Pandemic and lockdown	Shri B.M. Patil Medical College, Hospital and Research Center, BLDE(DU),KARNATAKA
54.	CTRI/2020/06/026152	COVID-19 in dialysis patients	Seth G.S. Medical College and KEM Hospital,MAHARASHTRA
55.	CTRI/2020/06/026262	Single Center,Study on Evaluation of use of,"AYURCOV" as add on therapy for Treatment of SARS-CoV-2 Infection in COVID-19 Patients,at Tertiary Care Center.	Department of Ayurveda ,Bhaktivedanta Hospital and Research Institute ,MAHARASHTRA
56.	CTRI/2020/05/025428	COVID -19 Pandemic and Lockdown : Impact on Parents Stress level, Infant care and follow-up	Department of Neonatology, Sri Ramachandra Institute of Higher Education and Research,TAMIL NADU
57.	CTRI/2020/05/025275	Role of Chyawanprash in the prevention of COVID-19 in health care workers	Ch. Brahm Prakash Ayurved Charak Sansthan,DELHI
58.	CTRI/2020/05/025274	Impact of remote audio-visual surveillance of doffing process during COVID 19 pandemic on the safety of health care workers	Nehru Hospital Extension PGIMER,CHANDIGARH
59.	CTRI/2020/05/025385	Research study to evaluate the impact of Selected Ayurvedic interventions in containment zone	Central Ayurveda Research Institute for Drug Development,WEST BENGAL Central Ayurveda Research Institute for Respiratory Disorders,PUNJAB Dr. Achanta Lakshmipati Research Centre for Ayurveda,TAMIL NADU National Ayurveda

			Research Institute for Panchakarma,KERALA National Ayurveda Research Institute for Panchakarma,KERALA Raja Ramdeo Anandilal Podar (RRAP) Central Ayurveda Research Institute for Cancer,MAHARASHTRA Regional Ayurveda Research Centre,NAGALAND Regional Ayurveda Research Institute for Drug Development,MADHYA PRADESH Regional Ayurveda Research Institute for Endocrine Disorders,RAJASTHAN Regional Ayurveda Research Institute for Endocrine Disorders,RAJASTHAN Regional Ayurveda Research Institute for Eye Diseases,UTTAR PRADESH Regional Ayurveda Research Institute for Gastro-Intestinal Disorders,ASSAM Regional Ayurveda Research Institute for

			Infectious Diseases,BIHAR Regional Ayurveda Research Institute for Infectious Diseases,BIHAR Regional Ayurveda Research Institute for Metabolic Disorders,KARNATAKA Regional Ayurveda Research Institute for Mother and Child Health,MAHARASHTRA Regional Ayurveda Research Institute for Nutritional Disorders,HIMACHAL PRADESH Regional Ayurveda Research Institute for Skin Disorders,GUJARAT Regional Ayurveda Research Institute for Skin disorders,ANDHRA PRADESH Regional Ayurveda Research Institute for Skin Disorders,GUJARAT
60.	CTRI/2020/05/025348	Medical students preference and perspective for online teaching during lockdown period	Kasturba Medical College, Manipal,KARNATAKA
61.	CTRI/2020/05/025341	A study to know the effect of Ayurvedic Kwath(Kiratiktadi Kwath) & Ashwagandha Churna along with yoga	GS Ayurveda Medical College & Hospital,UTTAR PRADESH

		exercises in the treatment of COVID-19 Positive patients.	
62.	CTRI/2020/05/025338	Evaluation of Efficacy and Safety of Ayurveda Intervention (Ayush -64) in the management of COVID-19 infection (Asymptomatic &Mild to Moderate symptoms	A and U Tibbia College and Hospital,DELHI
63.	CTRI/2020/05/025425	Ayurvedic intervention (Chyawanprash) in the prevention of COVID-19 pandemic among Health Care Personnel	Dept. of Panchakarma, A & U Tibbia College & Hospital,,DELHI
64.	CTRI/2020/08/026977	Comparison of two online learning method of resuscitation training.	All India Institute of Medical Sciences,DELHI
65.	CTRI/2020/08/027051	Survey of challenges faced by pain and palliative physicians working in cancer set up during corona virus disease time	Dr BRAIRCH, AIIMS, New Delhi,DELHI
66.	CTRI/2020/06/025861	Scientific evaluation of Immuno-modulatory effects of AYUSH INTERVENTIONS on normal healthy and high-risk individuals in context with COVID-19 pandemic: An open level study	Institutional Quarantine/ COVID Care Centre Almora,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Chamoli,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Champawat,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Dehradun,UTTARANCHAL Institutional Quarantine/ COVID Care Centre

			Garhwal,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Haridwar,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Nainital,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Pithoragarh,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Rudraprayag,UTTARANCHAL Institutional Quarantine/ COVID Care Centre Tehri,UTTARANCHAL Institutional Quarantine/ COVID Care Centre US Nagar,UTTARANCHAL
67.	CTRI/2020/06/025854	BCG vaccination against COVID-19	All India Institute of Medical Science, New Delhi,DELHI GS medical College & KEM Hospital,MAHARASHTRA ICMR-National Institute for Implementation Research on Non-Communicable Disease, Jodhpur,RAJASTHAN ICMR-National Institute for

			Research in Environmental Health,MADHYA PRADESH ICMR-National Institute for Research in Tuberculosis,TAMIL NADU ICMR-National Institute of Occupational Health,GUJARAT
68.	CTRI/2020/05/025431	A study to find our proportion of Covid 19 cases, need for hospital beds and utility of lockdown at Aurangabad	Government Medical College,MAHARASHTRA
69.	CTRI/2020/06/025556	A clinical trial to know the effect of Virulina® along with standard treatment in covid 19 positive patients.	Government Medical college & Government General Hospital,ANDHRA PRADESH
70.	CTRI/2020/05/025493	Effect of Ayurvedic medicine in the Prophylaxis for COVID-19 of Police personnel Dept of AYUSH, TS & CCRAS- NIIMH, Hyderabad.	Dr BRKR Government Ayurvedic College,TELANGANA
71.	CTRI/2020/06/026119	Efficacy of Arsenic Album 30C and 200C potency in mild case of COVID-19 positive . (Isolation ward of Sir T General Hospital, Bhavnagar) patients: A randomized controlled study.	Sir T General Hospital and Government Medical college and hospital, Bhavnagar,GUJARAT
72.	CTRI/2020/06/025525	Guduchi Ghanavati as a prophylactic measure among population at high risk to SARS-CoV-2 exposure	Akhandanand Ayurveda college,GUJARAT Government Ayurveda College Vadodara ,GUJARAT IPGTRA,GUJARAT

			Sheth J P Government Ayurved College,GUJARAT State Model Government Ayurved College,GUJARAT
73.	CTRI/2020/06/025529	Knowledge, Practice and mental health status of Spinal injured people	Centre for the Rehabilitation of the Paralysed (CRP),N/A
74.	CTRI/2020/06/025561	Effect of Ayurvedic medicine in the Prophylaxis for COVID-19 of AYUSH healthcare workers , Dept of AYUSH, TS & CCRAS-NIIMH, Hyderabad.	Dr. B.R.K.R. Government Ayurvedic College,TELANGANA
75.	CTRI/2020/08/027044	To observe the outcome of Classical Ayurvedic medicine for the treatment of COVID-19	Shri Krishna AYUSH University,HARYANA
76.	CTRI/2020/06/025761	Population based cross sectional study for COVID 19 prophylaxis with Polyherbal Siddha formulation Kabasura Kudineer / Nilavembu kudineer in containment zones and non containment zones during 2020 pandemic in Tamil Nadu, South India	Tambaram Taluk,TAMIL NADU
77.	CTRI/2020/06/025762	An Open-Label Randomized Controlled, Proof-of-Concept (PoC) Study to Evaluate the Safety and Efficacy of selected Siddha formulations in patients diagnosed with COVID-19	National Institute of Siddha & other Govt . approved COVID facilities and Quarantined houses ,TAMIL NADU
78.	CTRI/2020/06/025769	A prophylactic interventional study to determine the possible protective effect of Siddha Polyherbal formulation Kabasura Kudineer against the COVID	National Institute of Siddha,TAMIL NADU

		19 on intermittent, month-long consumption by public with close contacts to COVID patients and frontline workers in Tamil Nadu, India	
79.	CTRI/2020/08/027501	A study to assess aspects of safety and efficacy of Nuvastatic™ (C5OSEE5050ESA) as an immunomodulator supportive treatment to the standard care of treatment in Covid 19 patients.	Navin Hospital,UTTAR PRADESH
80.	CTRI/2020/06/025763	A Randomized controlled Clinical Trial to determine the efficacy of Siddha drugs in COVID 19 patients	SRM Medical college Hospital and Research centre,TAMIL NADU
81.	CTRI/2020/06/025613	Melatonin Immune Boost COVID 19 Study	All India Institute of Medical Science Rishikesh ,UTTARANCHAL
82.	CTRI/2020/06/025855	Effect of AYUSH 64 in COVID 19	IPGT and RA Hospital Jamnagar,GUJARAT Guru govind singh government hospital Jamnagar ,GUJARAT
83.	CTRI/2020/07/026389	Effect of Corona virus infection and lockdown on access to health services and on mental health among urban and peri-urban low- to mid-socioeconomic neighborhoods in South Delhi	Centre for Health Research and Development, Society for Applied Studies ,DELHI
84.	CTRI/2020/06/025673	A study on association between tobacco and COVID 19 to help policy makers	Kasturba Medical College, Manipal,KARNATAKA
85.	CTRI/2020/08/026978	Effectiveness of Ayurvedic Formulation for COVID 19	Nepal Health Research Council,N/A
86.	CTRI/2020/06/025760	A clinical trial to study the effect of drug named	Vijaya Medical and Educational Trust,TAMIL

		Sofosbuvir in hospitalized patients with COVID 19.	NADU
87.	CTRI/2020/06/025768	An open label Randomized Controlled Clinical trial to Evaluate the Safety and Efficacy of selected Siddha formulations in patients diagnosed with COVID-19	Chengalpattu Medical College Hospital,TAMIL NADU
88.	CTRI/2020/06/025779	Study of AYUSH KWATH in quarantine persons	COVID 19 Quarantine Centre,RAJASTHAN
89.	CTRI/2020/06/025803	Effect of convalescent plasma in COVID-19 patients	Institute of Liver and Biliary Sciences,DELHI Maulana Azad Medical College,DELHI Rajiv Gandhi Super Speciality Hospital,DELHI
90.	CTRI/2020/06/025800	Role of Ayurveda in Covid 19 management.	Lokbandhu Rajnarayan Combined Hospital,UTTAR PRADESH Ramsagar Mishra 100 bed Hospital,UTTAR PRADESH
91.	CTRI/2020/07/026943	Effects of revised COVID19 specific infection control protocol on the well being of dental professionals	Manipal College of Dental Sciences, Manipal,KARNATAKA
92.	CTRI/2020/06/026227	A Study on Unani regimen for prevention of high/moderate risk population of COVID 19	Regional Research Institute of Unani Medicine,DELHI
93.	CTRI/2020/06/025848	Clinical Analysis of Patients Hospitalized Due To Covid-19	Topiwala National Medical College and BYL Nair Ch Hospital,MAHARASHTRA
94.	CTRI/2020/07/026676	Psychological Impact of COVID 19 on Pregnant women	CARE Hospital - Hitech Branch,TELANGANA
95.	CTRI/2020/06/025856	Evaluation of siddha regimen in the management of covid	Government medical college,TAMIL NADU

96.	CTRI/2020/07/026301	Role of Yoga in deStressing HCWs in COVID-19 : A RCT	AIIMS Rishikesh,UTTARANCHAL
97.	CTRI/2020/06/025858	Observational study on suspected COVID 19 patients admitted to ICU	St Johns Medical college,KARNATAKA
98.	CTRI/2020/06/025857	Follow-up of COVID-19 Positive Patients	Jashore University of Science and Technology,N/A
99.	CTRI/2020/06/026045	A study to improve the resistance against Covid 19 illness with the help of Homoeopathic remedies.	Father Muller Homoeopathic Medical College and Hospital,KARNATAKA
100.	CTRI/2020/06/025874	To observe the effect of Siddha formulation Kabasura kudineer in COVID 19 patients	Government Theni Medical College and Hospital,TAMIL NADU
101.	CTRI/2020/07/026664	To find the frequency of misting "fogging"of protective spectacles and comparison of various techniques to reduce misting of spectacles while working in intensive care unit during COVID 19 pandemic	St Johns Medical College Hospital,KARNATAKA
102.	CTRI/2020/06/025957	A Clinical Study on Favipiravir and Umifenovir Compared to Favipiravir alone in Hospitalized Patients with Moderate COVID-19.	All India Institue of Medical Sciences-Nagpur ,MAHARASHTRA Apollo Speciality Hospitals,TAMIL NADU Bangalore Medical College and Research Institute,KARNATAKA D Y Patil Hospital,MAHARASHTRA Dr LH Hiranandani

			Hospital,MAHARASHTRA GMERS Hospital,GUJARAT Government medical college and hospital-Aurangabad,MAHARASHTRA Government Medical College and Hospital-Nagpur,MAHARASHTRA Indraprastha Apollo Hospital,DELHI Metas Adventist Hospital,GUJARAT MGM medical College & Hospital,MAHARASHTRA Noble Hospitals Pvt. Ltd,MAHARASHTRA Rajiv Gandhi Medical College & Chatrapati Shivaji Maharaj Hospital,MAHARASHTRA Ram Manohar Lohia Hospital,DELHI Ruby Hall Hospital,MAHARASHTRA Seth Nandlal Dhoot Hospital ,MAHARASHTRA Sir Gangaram Hospital,DELHI SMS Medical College &

			Hospital,RAJASTHAN Smt. Kashibai Navale Medical College & General Hospital,MAHARASHTRA St. George Hospital,MAHARASHTRA Yashwantrao Chavan Memorial Hospital,MAHARASHTRA
103.	CTRI/2020/06/025999	Clinical trial of ShatPlus as an immunomodulator in adult Covid 19 positive patients	Pimpri Chinchwad Municipal Corporatios YCM Hospital ,MAHARASHTRA
104.	CTRI/2020/06/026193	A study of drug Lithium on patients of Covid 19 disease	Lok Nayak Hospital,DELHI
105.	CTRI/2020/07/026788	A Qualitative study regarding stress and coping in Front-line Health Care Doctors at a tertiary-care hospital.	B.J.,Government Medical College,MAHARASHTRA
106.	CTRI/2020/07/026832	Artificial intelligence and machine learning for Covid 19	Rajarajeswari Medical college and Hospital,KARNATAKA
107.	CTRI/2020/06/026002	Study of use of Ayurveda Intervention (Ayush-64) in COVID 19	All India Institute of Medical Sciences, Jodhpur,RAJASTHAN
108.	CTRI/2020/06/026118	Antiphospholipid Antibody (APLA) level in COVID-19 Cases.	KIMS COVID Hospital, BBSR,ORISSA
109.	CTRI/2020/07/026714	Psychological Impact of COVID 19 on Healthcare Workers	CARE Hospital Hitech Branch,TELANGANA
110.	CTRI/2020/06/026120	Validation of Rapid Test kit for Antibody (IgG, IgM) detection against COVID19.	Maulana Azad Medical College, new Delhi,DELHI
111.	CTRI/2020/07/026339	Understanding COVID and cancer	Tata Memorial Hospital,MAHARASHTRA

112.	CTRI/2020/07/026516	Clinical manifestations in neonates born to Covid 19 positive mothers.	,GMC Aurangabad,MAHARASHTRA
113.	CTRI/2020/06/026188	Psychological Assessment of adult COVID-19 patients	Kalinga Institute of Medical Sciences ,ORISSA
114.	CTRI/2020/06/026187	Clinical trial of herbal supplement as an immunomodulator in adult Covid 19 positive patients.	Pimpri Chinchwad Municipal Corporations YCM Hospital,MAHARASHTRA
115.	CTRI/2020/06/026189	To Compare the safety and efficacy of Vitamin D, with Magnesium in mild to moderate Covid 19 patients	A C Subba Reddy Medical Hospital,ANDHRA PRADESH
116.	CTRI/2020/06/026191	To study the safety and efficacy of Vitamin D3, Vitamin K2-7 & magnesium , in prevention of COVID 19 infection in health care professional (HCP)	A C Subba Reddy Medical Hospital,ANDHRA PRADESH
117.	CTRI/2020/07/026705	Efficacy and safety of AYUSH 64 tablets in treating mild to moderate Covid 19 patients	Hassan institute of Medical sciences,KARNATAKA Shri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital ,KARNATAKA
118.	CTRI/2020/07/026836	Effect of COVID - 19 pandemic researchers	Manipal College of Nursing,KARNATAKA
119.	CTRI/2020/07/026534	Study of antiviral nutraceutical PICOVRID in COVID 19 patients	Government Medical College Nagpur,MAHARASHTRA
120.	CTRI/2020/07/026790	This is the comparative study between two protective boxes which can be used by the doctors while managing critical COVID 19 patients in addition to personal protective equipment.	Medical Education Department ,UTTARANCHAL
121.	CTRI/2020/06/026232	Ivermectin in the prevention of covid-19	DVPM,ANDHRA PRADESH

122.	CTRI/2020/07/026354	Clinical trial of ozone therapy in mild to moderate Covid-19 subjects.	Lokmanya Hospital,MAHARASHTRA
123.	CTRI/2020/07/026343	Ayurvedic Rasayana treatment as an addon therapy to improve the results in management of coronavirus disease	Yashwantrao Chavan Memorial Hospital ,MAHARASHTRA
124.	CTRI/2020/07/026700	Ayurvedic Rasayana therapies	Symbiosis Medical collage for woman ,MAHARASHTRA Yashwantrao Chavan Memorial Hospital YCM Hospital Rd Sant Tukaram Nagar Pimpri Colony Pune ,MAHARASHTRA
125.	CTRI/2020/07/026368	Spread of corona virus disease and factors affecting it in Pune city.	B J Govt Medical College Pune,MAHARASHTRA
126.	CTRI/2020/07/026433	Effect of Ayurveda medicinein Covid-19 mild symptoms	Civil Hospital,GUJARAT
127.	CTRI/2020/07/026528	Herbal formulation for immunity boosting during pandemic	Shree Saptashrungi Ayurved Mahavidyalaya and Hospital,MAHARASHTRA
128.	CTRI/2020/07/026355	Evaluation Of The Efficacy of AYUSH KWATH in The Prevention of COVID-19	Hot spot area ,RAJASTHAN
129.	CTRI/2020/07/026424	An Observational Study on Health issues during covid 19 lock down	Area of Jodhpur City,RAJASTHAN
130.	CTRI/2020/07/026431	A clinical trial to find out the effectiveness of traditional awareness method and anticipatory guidance through motivational interviewing.	KVG Dental College and Hospital,KARNATAKA
131.	CTRI/2020/07/026560	Neem Prophylaxis for Subjects Coming in Contact	Department of AYUSH, ESIC Medical College and

		with COVID-19 Patients	Hospital,HARYANA
132.	CTRI/2020/07/026571	Pattern of ocular surface involvement in COVID-19 patients in Hassan,Karnataka.	Hassan institute of medical sciences hasaan(COVID HOSPITAL),KARNATAKA
133.	CTRI/2020/07/026473	Views of Indian dental students on international dental higher education after Covid-19	Manipal College of Dental Sciences, Manipal,KARNATAKA
134.	CTRI/2020/07/026926	Ethics of Behavioral Interventions during the Covid 19	Jawaharlal Institute of Postgraduate Medical Education and Research,PONDICHERRY PSG Institute of Medical Sciences & Research,TAMIL NADU Sanjay Gandhi Postgraduate Institute of Medical Sciences,UTTAR PRADESH Seth GS Medical College and KEM Hospital,MAHARASHTRA Tata Memorial Hospital,MAHARASHTRA
135.	CTRI/2020/07/026631	Uses of herbal combination by taking it in hot water in covid 19 positive patients.	johnson clinic,TAMIL NADU Murugaa hospital fertility centre,TAMIL NADU Pranav clinic,TAMIL NADU
136.	CTRI/2020/07/026575	Sahadevi Choorna for COVID 19	Parul Sevasharma Hospital,GUJARAT
137.	CTRI/2020/08/027001	association of cardiac markers with severity of covid 19	post graduate institute of medical education and

			research,CHANDIGARH
138.	CTRI/2020/07/026530	Ayurvedic formulations for the prevention of COVID-19 infection	Thanjavur Medical College,TAMIL NADU
139.	CTRI/2020/07/026559	Survey about knowledge towards blood donation during COVID 19 pandemic	Blood Bank, Kasturba Hospital, Manipal,KARNATAKA
140.	CTRI/2020/08/027174	Psychological Impact of COVID 19 on frontline health care workers	AIIMS Jodhpur,RAJASTHAN
141.	CTRI/2020/07/026514	Randomized Controlled Trial Of Resveretrol-Copper OR Sodium-Copper-Chlorophyllin Versus Standard Treatment In Severe Covid-19 Cancer Patients.	Tata Memorial Hospital,MAHARASHTRA
142.	CTRI/2020/07/026630	Clinical trial of ACT 12 tablet and ACT 13 dry syrup in Covid 19 patients	Lokmanya Hospital,MAHARASHTRA Naidu Hospital,MAHARASHTRA
143.	CTRI/2020/07/026515	Randomized Controlled Trial Of Resveretrol-Copper Or Sodium-Copper-Chlorophyllin Vs Standard Treatment In Mild Covid-19 infection with Cancer Patients.	Tata Memorial Hospital,MAHARASHTRA
144.	CTRI/2020/07/026925	to see the effect of twakadi(tea made up of dalcheeni, tulasi pepper, clove, etc)tea on police worker who have a duty in covid 19 pandemic	Sterling Multispeciality Hospital and Ayurved Rugnalay,MAHARASHTRA
145.	CTRI/2020/07/026792	Affect in surgical care in children due to COVID 19 in India: a online survey of surgeons	Chacha Nehru Bal Chikitsalaya,DELHI
146.	CTRI/2020/07/026669	Unani Herbal tablets for mild cases od Covid 19	Covid Care Center,MAHARASHTRA

147.	CTRI/2020/08/027475	A Randomized Controlled Trial Of An Immunomodulator Mycobacterium w In Mild To Moderate Covid-19 Pneumonia	Care Hospital,Banjara Hills,TELANGANA
148.	CTRI/2020/07/026841	A clinical trial to study the effects of an Ayurvedic medicine, Haldi 30 (Turmeric extract) drops in patients with Corona virus infection.	Sahyadri Hospital, Kothrud branch 2,MAHARASHTRA Sahyadri Superspeciality Hospital, Deccan Gymkhana branch 1,MAHARASHTRA
149.	CTRI/2020/07/026953	COMPARISON OF THREE HOMOEOPATHIC DRUGS FOR COVID 19 IMMUNE BOOSTERS AGAINST STANDARD TREATMENT	National Institute of Homoeopathy ,WEST BENGAL
150.	CTRI/2020/07/026673	Siddha formulations for the prevention of COVID-19 infection	THANJAVUR MEDICAL COLLEGE HOSPITAL,TAMIL NADU
151.	CTRI/2020/07/026632	Siddha Treatment for COVID 19- a Pilot Study	Dr Ambedkar Arts College Siddha COVID Care Center,TAMIL NADU
152.	CTRI/2020/07/026942	Study of COVID 19 suspected pregnant women	Kasturba Medical College, Manipal Academy of Higher Education,KARNATAKA
153.	CTRI/2020/07/026674	Effect of Ayurveda Spice Mix Tablet for the Prevention of COVID-19 infection in people exposed to Covid 19 and in high risk patients	Ashtang Ayurveda Mahavidyalaya,MAHARASHTRA
154.	CTRI/2020/07/026793	Panchgavya Therapy in prophylaxis and as an adjuvant therapy in management of Covid 19.	Lokmanya Hospital,MAHARASHTRA
155.	CTRI/2020/08/027000	Retrospective cohort study in COVID 19 recovered patients	Central Council for Research in Homoeopathy,DELHI
156.	CTRI/2020/07/026671	Ozone Therapy for Covid 19	NeuroGen Brain and Spine

		patients	Institute,MAHARASHTRA
157.	CTRI/2020/07/026675	Efficacy of Ayurveda treatment Protocol with Tulsimmune Tablet in Covid 19	H.J. Doshi Ghatkopar Hindusabha Hospital,MAHARASHTRA
158.	CTRI/2020/07/026677	Role of cough and voice analysis using artificial intelligence in the management of COVID 19 patients	CARE Hospital,TELANGANA Gandhi Medical college and Hospital,TELANGANA
159.	CTRI/2020/07/026715	Structured online training program on specific COVID-19 Airway Management	AIIMS Hospital,UTTARANCHAL
160.	CTRI/2020/07/026794	Vitamin-D levels in COVID-19 Patients and their relationship with other bone metabolism markers	AIIMS Raipur,CHHATTISGARH
161.	CTRI/2020/08/027470	Anaesthesia practices and safety of caregivers during the covid 19 pandemic.	Max Super Speciality Hospital,DELHI
162.	CTRI/2020/07/026759	Detection of Antibodies to COVID-19	Medanta The medicity,HARYANA
163.	CTRI/2020/07/026922	Ayurvedic intervention in COVID-19 patients	Lokbandhu Rajnarayan Combined Hospital,UTTAR PRADESH
164.	CTRI/2020/07/026843	Use of new technology for rapid detection of SARS-CoV2	Akash Healthcare Superspecialty Hospital ,DELHI Dr Ram Manohar Lohia Hospital,DELHI Institute of Nuclear Medicine & Allied Sciences (INMAS),DELHI Lady Hardinge Medical College,DELHI Lok Nayak Jai Prakash Hospital,DELHI

			Sir Gangaram Hospital,DELHI
165.	CTRI/2020/07/026902	Effect of CRP blood test in management of COVID 19 patients	Microbiology Department GCS Medical College Hospital and Research centre,GUJARAT
166.	CTRI/2020/07/026821	Study of skin, hair and nail changes after COVID 19 illness.	GCS Medical College, Hospital & Research Centre,GUJARAT
167.	CTRI/2020/08/027469	A survey to understand the opinion among doctors regarding usage of personal protective equipment	Karnataka Institute of Medical Sciences, Hubballi,KARNATAKA
168.	CTRI/2020/08/027173	Necessary measures taken for covid positive pregnant women during pandemic.	BLDE HOSPITAL AND RESEARCH CENTER,KARNATAKA
169.	CTRI/2020/07/026954	Study of blood tests findings in patients of COVID 19 in a tertiary care centre	GCS Medical College Hospital and Research Centre,GUJARAT
170.	CTRI/2020/08/026980	Effect Ayurveda decoctions, tablet and Panchagavya on COVID 19	ims bhu ,UTTAR PRADESH
171.	CTRI/2020/08/027323	A survey to collect vital parameters and symptoms of participants at risk of COVID19	Kailash Hospital,GUJARAT Rhythm Heart Institute- A Unit of SLPL,GUJARAT
172.	CTRI/2020/08/027008	Advantage of Artificial Intelligence to detect COVID 19 using Chest X-Ray.	GCS Medical College and Hospital,GUJARAT
173.	CTRI/2020/08/026981	Study of changes in levels of certain blood parameters in covid-19 patients	GCS Hospital College and Research center ,GUJARAT
174.	CTRI/2020/08/026962	Incubation period of COVID-19 cases admitted in North Kerala, India	Government Medical College Kannur Kerala,KERALA
175.	CTRI/2020/08/027244	Behavioural and emotional difficulties of school going children during COVID times	Lokopriya Gopinath Bordoloi Regional Institute of Mental Health,ASSAM
176.	CTRI/2020/08/027046	A survey to analyze the	Kasturba Medical College,

		understanding about the use of face mask among the general public during COVID 19	Kasturba Hospital, Maniapl Academy of Higher Education,KARNATAKA
177.	CTRI/2020/08/027041	Clinical trial on COVID 19 patients to Improve Immunity	Government Medical college & Government General Hospital,ANDHRA PRADESH Shettys Hospital ,KARNATAKA
178.	CTRI/2020/08/027110	The role of markers(nlr,il-6,d-dimer) in COVID-19 patients and it's co-relationship with oxygenation ,a retrospective observational study in Tertiary care covid ICU	Vmmc and Safdarjung Hospital,DELHI
179.	CTRI/2020/09/027614	Effectiveness of training programme on hand hygiene among laundry staff	Government Medical College Kannur,KERALA
180.	CTRI/2020/08/027042	Secondary attack rate of COVID 19, Kerala	Government Medical College Kannur Kerala,KERALA
181.	CTRI/2020/08/027085	Safety and efficacy of citrobioShield product in improving immunity in COVID 19 patients via inhalation.	Mourya Multisoeciality Hospital,MAHARASHTRA
182.	CTRI/2020/08/027081	Comparision of two barrier devices for placement of tube into trachea(windpipe)in COVID19 patients	GCS Medical College,Hospital & Research Centre Ahmedabad-380025,GUJARAT
183.	CTRI/2020/08/027164	National Clinical Registry of COVID 19	AIIMS Jodhpur,RAJASTHAN
184.	CTRI/2020/08/027047	Nursing students perception of out of the classroom learning during the period of COVID-19	Manipal College of Nursing,KARNATAKA
185.	CTRI/2020/08/027275	The study of occurrence , distribution and control	B J GOVT MEDICAL COLLEGE AND SASSOON

		measures of COVID-19 among police personnel during pandemic in Pune city , Maharashtra	GENERAL HOSPITALSPUNE ,MAHARASHTRA
186.	CTRI/2020/08/027286	Effectiveness of Siddha Medicines Kabasura Kudineer and Nilavembu Kudineer in the Management of Smptomatic COVID 19 patients	Government Institute of Medical Sceinces,UTTAR PRADESH
187.	CTRI/2020/08/027283	A clinical trial to evaluate the medicinal efficacy and safety of Ayurvedic kit in COVID-19 positive Patients.	BANGALORE MEDICAL COLLEGE & RESEARCH INSTITUTE,KARNATAKA
188.	CTRI/2020/09/027572	"Effect of comorbidities in the outcome of COVID-19 patients, a study in tertiary care centre ICU in India"	VMMC and Safdarjung Hospital,DELHI
189.	CTRI/2020/09/027615	Clinical trial of homeopathic medicine arsenic album as add on therapy in hospitalized patients admitted with Covid 19 disease.	Mgm mcri hospital Aurangabad,MAHARASHTRA
190.	CTRI/2020/08/027225	Ivermectin as a possible treatment for COVID-19	AII India Institute of Medical Sciences, Patna,BIHAR
191.	CTRI/2020/08/027282	Prophylactic Ivermectin in COVID 19 Contacts	Government Institute of Medical Sciences,UTTAR PRADESH
192.	CTRI/2020/08/027500	Study for predicting hypoxemia in COVID 19 patients on the basis of HRCT thorax findings with correlating the CT findings with SpO2 levels.	Department of radiodiagnosis, Kalinga institute of medical sciences , Patia , Bhubaneswar. ,ORISSA
193.	CTRI/2020/08/027359	A study regarding knowledge, attitude and practice about immunity boosting measures for prevention of COVID-19	Shree Krisha Hospital ,GUJARAT

		infection among healthcare workers at tertiary care hospital	
194.	CTRI/2020/08/027394	Assessment of response of ivermectin on virological clearance in COVID 19 patients	maulana azad medical college and associated LN hospital ,DELHI
195.	CTRI/2020/09/027622	Role of female sex hormone in COVID 19 patients	Government institute of medical sciences,UTTAR PRADESH
196.	CTRI/2020/08/027403	A retrospective assessment of risk factors for COVID- 19 in health care workers	Lok Nayak Hospital,DELHI
197.	CTRI/2020/09/027517	Management of cardiac disease during COVID 19 pandemic and impact among cardiologist in Tamil Nadu	C3 Research Foundation,TAMIL NADU
198.	CTRI/2020/09/027683	Online survey on Dry eye symptoms in health care workers and children during COVID 19 pandemic	Chacha Nehru Bal Chikitsalya,DELHI
199.	CTRI/2020/09/027544	Covid 19 and Professional course students quality of life	Haldia Institute of Dental Sciences And Research,,WEST BENGAL
200.	CTRI/2020/09/027548	Effects of health drink additional to standard of care treatment in COVID 19 patients.	SPARSH Super Speciality Hospital,KARNATAKA
201.	CTRI/2020/09/027616	Oral medicine trial for COVID 19	Ayurveda Mahavidyalaya ,KARNATAKA
202.	CTRI/2020/09/027596	Behavioral changes during COVID 19 among cricket players in India	C3 Research Foundation,TAMIL NADU
203.	CTRI/2020/09/027661	Preventive Study among COVID 19 frontline warriors and their families	Central Ayurveda Research Institute for Hepatobiliary Disorders,OPD Room no 3,ORISSA
204.	CTRI/2020/09/027687	Assessment of effect of steam inhalation, saline gargling	Bangalore Medical College and Research

		and povidone Iodine gargling on reduction of symptoms and prevention of spread of COVID 19	Institute ,KARNATAKA
205.	CTRI/2020/09/027688	Testing efficacy of Homoeopathic Medicine Camphora 1000 C as an immune booster, reducing the incidence of coronavirus infection.	DKMM Homoeopathic Medical College and Hospital,MAHARASHTRA

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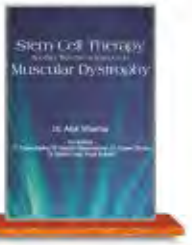

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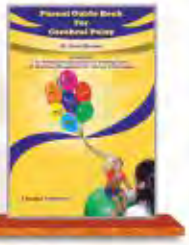

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