



**INDIAN MEDICAL ASSOCIATION
ACADEMY OF MEDICAL SPECIALITIES
(IMA AMS)**

Head Quarters, Hyderabad, Telangana



Annals 2021 National AMSCON

**Theme :
COVID-19**

**December 19-20, 2021
Tirupati, Andhra Pradesh**

Prof. Dr. J. A. Jayalal
National President

Dr. Sahajanand Prasad Singh
National President Elect

Dr. Jayesh M Lele
Hon. Secretary General

Dr. Anil Goyal
Hon. Finance Secretary

Dr. D. Shreehari Rao
National Chairman, IMA AMS

Dr. Sanjeev Singh Yadav
Hon. National Secretary, IMA AMS

Dr. Srirang Abkari
Hon. Editor (Annals) IMA AMS

**IMA ACADEMY OF MEDICAL SPECIALITIES
Head Quarters, Hyderabad, Telangana**

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INDIAN MEDICAL ASSOCIATION

Headquarters, New Delhi



1492 modern medicine doctors have sacrificed their lives in the service of the nation in the COVID 19 pandemic. Many have left behind families and children who require help for sustenance, education and upbringing.

We care IMA cares India cares

We will NEVER let you down

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“IMA COVID MARTYRS FUND”
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Dr. Ketan Desai
Past President, WMA

Dr. J A Jayalal
National President

Dr. Jayesh Lele
Hon. Secy. General

Dr. Anil Goyal
Hon. Finance Secretary

IMA PRAYER



May everybody be happy
May everybody be healthy
May everybody be free from pain
May everybody be free from sorrow
May we be the healing cure
Beyond every greed & lure

FLAG SALUTATION

We, the members of Indian Medical Association
Stand here to salute our National Flag.
Its honour and glory shall be our light and strength
And its course shall be our course.
We pledge our allegiance to it and realizing our responsibilities
As the accredited members of this National organization,
We swear we will dedicate everything in our power
To see it fly high in the comity of Nations.
Jai Hind!

Foreword



Dr. Vedprakash Mishra
Pro Chancellor
Datta Meghe Institute of Medical Science,
Nagpur

Human history is plagued by Pandemics of wide and varied magnitude that have resulted in devastation beyond imagination. 21st Century got gripped under the spell of Covid-19 pandemic in a mode and manner that shattered the roots of health care delivery system and left it helter skelter across the world. It was a thunder which jolted the entire world in a unprecedented manner. The spell baffles imagination in all its aspects as the devastation resulted is beyond comprehension.

It is not that the pandemic did not yield an opportunity for professional scientific community to peep into its wide and varied aspects and put into place the required sucker in the interest of men and mankind. It's a matter of established reality that the nature extent magnitude of the pandemic was mind boggling. Yet the human endeavors and the initiatives plagued by inquisitive commitment and extraordinary resilience did rise to the occasion and substantial relief thereto is visible.

It is in this backdrop the initiative of compilation of the research in wide and varied aspect of Covid-19 carried out by the leading professional scientists in different parts of the country needed to be put into a common compendium so that it turns out to be a handy reference for several desired targeted purposes.

The present venture of compilation of the research articles on the wide ranging aspects of Covid-19 including Epidemiology, Diagnostics, therapeutics and also prognostics speaks volumes about its significance, importance and relevance and impact. As such, the compilation so generated would be serving as handy handbook not only for easy use and utility but would also facilitate invocation of the holistic outlook towards the problem and also resultant holistic effective, cogent, credible management of the same. It is indeed a great effort and a laudable initiative for which words find themselves at bay to bring out the desired and required appreciation of the same. My salutation to all the contributors and full marks the initiative undertaken for compilation of the same so as to make it easily available for its targeted use and desired utility.

Dr. Vedprakash Mishra

From the Editor's Desk



Dr. Srirang Abkari
Honorary Editor - ANNALS
IMA AMS, Hqrs

Annals derived from the Latin word annales, are a concise historical record in which events are arranged chronologically, year by year. The Academy of Medical Specialities is the academic wing of the Indian Medical Association with the following objectives:

- To acknowledge talent, expertise and experience in all specialties, medical and surgical, including basic medical sciences;
- To formulate policies and make suggestions and recommendations in the matter of medical education and training, in particular encouraging continuing educational activities;
- To promote teaching, training and Continuing Medical Education of its members on an ongoing basis;
- To devise ways and means to encourage group studies, co-operative activities, research projects in both the methodology of educational techniques and field research into diseases/disease complexes, etc.
- To compile, educational material, including publication of literature, periodicals, bulletins and books.

The Annals of IMA AMS this year therefore aims to fulfill these very objectives. It acknowledges the talent, expertise and experience of all the distinguished clinicians who have authored the chapters in this issue. This special issue will promote teaching, training and continuing medical education on a very pertinent topic. It is a compilation of a very relevant educational material which I am sure will stimulate research on this burning subject and finally we can collectively make suggestions and recommendations for medical education and training of our medical fraternity.

In the last two years we have witnessed the evolution, establishment and spread of a pandemic right in front of our eyes. This has been a most difficult period for mankind and a gentle reminder of our frailty in this day and age of technological advancement. There couldn't have been therefore a more apt theme for the Annals than that of COVID-19. Words which were alien to most are now everyday vocabulary in households. They include "quarantine, isolation, mask, n95, sanitizer, RT PCR, Crp, D-Dimer, remdesivir, corona virus, covid, Wuhan, oxygen concentrator, pulse oximeter, HRCT, CT value, CORAD" and the list goes on. The irony is that, even after 266,504,411 cases and 5,268,849 deaths world-wide we do not know the origin of the virus!

It was initially thought that the virus may not spread from the country of its origin, there was not enough evidence of human to human transmission, masks were not advocated for all and lockdowns began a bit too late. The novel corona virus by then had spread its tentacles the world over and brought in a phase of death and despair. It was a "shock and awe" all-out attack and humanity was pushed to its knees. The saddest part was to suffer and die in isolation, far from the warmth and comfort of our loving ones. I don't recollect any disease in human history where such a large number of medications have been used in the hope of cure. The list is very long but to name a few- hydroxychloroquine, azithromycin, doxycycline, vitamin c, vitamin d, zinc, steroids, ivermectin, colchicine, remdesivir, favipiravir, lopinavir-ritonavir, convalescent plasma, tocilizumab, baricitinib and finally the antibody cocktail. We are all aware that except for steroids, the antibody cocktails and may be remdesivir, there is little evidence of benefit with the others. Humans scampering for oxygen in the 21st century and the last rites being performed without kith and kin around are probably the most distressing images we can recollect.

However, amid the gloom and despair, there stood out the brave and selfless frontline warriors. Leading the pack were the medical professionals who sacrificed everything, treated when no cure existed, cared when no one dared and were the rays of hope for the entire humanity. The world understood and acknowledged the herculean effort of these white coat soldiers. The claps at 5pm on 22nd March 2020 in India on the day of Janata Curfew were truly from the heart to express gratitude to these untiring professionals. The supreme sacrifice of the 1492 doctors of Modern Medicine for India and its citizens deserves better recognition. Working in suffocating conditions, without food and water for unknown ones, truly epitomizes the spirit of our medical profession and I salute all the doctors, nurses, paramedical staff and health care workers. To listen to someone and speak a few reassuring words sometimes makes a difference between life and death for a patient and our doctors have definitely risen to the occasion and given comfort and solace to those infected. Our scientists too need a big applause for the sheer rapidity with which they have successfully developed safe and effective vaccines which now are the main reason for the decline in the cases. The government needs to be appreciated for achieving a gigantic task of vaccinating 130 crore citizens.

The commendable role the Indian Medical Association has played during the pandemic needs to be applauded and I thank the entire leadership for this. We look forward to their continual guidance and promise to stand united in all our endeavors.

This issue of the Annals on COVID-19 is a result of inspiration and guidance from the seniors, support and encouragement from colleagues and dedication and sincerity from all the eminent authors and co-authors who have shared knowledge, wisdom and their vast real life experience so that the reader can easily understand and learn and ultimately pass on the benefit for the betterment of the patient. We have made every effort to maintain the highest academic standards and to prepare an issue which is comprehensive yet precise, which will be highly sought after by all specialties and will truly enrich the understanding of the members of our fraternity on this complex subject.

I am indebted to our visionary leader Dr. Ketan Desai for his blessings and for giving this important responsibility. I am thankful to our dynamic National President Dr. J A Jayalal and the very efficient Honorary Secretary Dr. Jayesh M Lele for guiding and inspiring us to seek academic excellence. My

sincere thanks to our caring Chairman IMA AMS, Dr. D.Sree Hari Rao, and the live-wire Honorary Secretary IMA AMS Dr. Sanjeev Singh Yadav, for the constant encouragement, help and unstinted support given in preparing this issue. My heartfelt thanks to all the office bearers, members of the Editorial Board of IMA AMS for their best wishes and whole-hearted support. My special thanks to Mrs. Sarita from our AMS office for the immense help in coordinating with the authors and Mr. Kantilal Shah and Mr. Murali of Atlas Stationary & Printing Industries for making this Annals a reality.

I would like to acknowledge the great work done by my predecessors and all the past Chairmen and Secretaries of IMA AMS in laying the foundation and building the IMAAMS into a very vibrant wing.

Such testing times reveal the true character of an individual as well as an organization and we can proudly say that medical professionals and the Indian Medical Association have displayed remarkable statesmanship, courage, resilience, and empathy during this pandemic.

And even as we began heaving a sigh of relief that the cases are coming down and that the vaccinations are going up, the virus quickly reemerged in South Africa as a new variant of concern B.1.1.529 on 24th November 2021, was designated as Omicron and within a short while has already spread to 57 countries. Therefore we must adhere to COVID appropriate behavior at all times and remain vigilant. We await more data on the infectivity, virulence and immune escape potential of this new variant.

Once again I pay my tributes to the COVID Martyrs and urge all of you to generously contribute to the COVID Martyrs Fund.

Long Live IMA!

Dr. Srirang Abkari

Honorary Editor - ANNALS

Messages

Message



Dr. J A Jayalal
National President
IMA Head Quarters

To,
Dr. Sanjiv Singh Yadav
Honorary Secretary
IMA AMS HQs

Respected Sir,

I deem it a privilege to bring greetings to you all from IMA HQ on this jubilant occasion of much awaited annual conference of Academy of Medical Specialties and release of our prestigious Annals of AMS, to be held in the spiritual Tirupathi on 19th & 20th December 2021.

I am delighted to see the vibrancy with which the much-respected doctor and tall leader Dr. Daggumati Srihari Rao as Chairman, you as a dynamic Secretary coordinated and maintained the tempo of academic propagation and sustained the objectives of Academy of Medical Specialty through this turbulent year of Corona.

Knowledge is power and appropriate dissemination of the updated skills and knowledge to our members is the priority of AMS. By empowering our colleagues with enhanced knowledge, we indirectly serve the common people as knowledge conceived by our members are not going to get stagnated with them but will flow and percolate into the community and people who seek remedy for their ailments through them will definitely reap the fruit. There is no limit for this propagation. The beauty of this year, with the aid of Zoom meet it has given an all-India color to our Academy and almost all states were roped in by the majestic and persuasive works of Chairman and Secretary to take part actively in this mission. The Zonal conferences organised by you were a real academic feast to many.

I also take this opportunity to congratulate our Chairman of 2020 Dr. M.S. Ashraf for the excellent spade works in the biennium.

I wish and hope IMA AMS must grow as a much-respected academy of International Status and research initiatives must flow out of it and be in a position to guide, formulate and plan the future direction of Health Care.

I am happy to inform our IMA Headquarters have established an independent ethics committee registered with ICMR and CDSCO, hence we can take up pan- India research, including drug trials.

Hope AMS will rise upto the situation.

I thank the team of Editors, leaders and contributors for this prestigious Annals of AMS.

Yours in Service,

Prof. Dr. J.A. Jayalal

National President, IMA

DR. SAHAJANAND PRASAD SINGH

MBBS, MS (Gen. Surgery), FCGP, FIAMS

Associate Professor, Dept. of Surgery, VIMS, Pawapuri

National President (Elect), Indian Medical Association (HQs.)

Member, National Medical Commission, New Delhi

Dr. B. C. Roy Awardee

Registrar, Bihar Council of Medical Registration

Former Chairman, Election Commission, IMA HQs.

Former President, IMA Bihar State Branch

Former Member of Medical Council of India



MESSAGE

To,

Dr. Sanjeev Singh Yadav

Organising Secretary

IMA AMS NATCON 2021

Tirupati.



Sir,

It is a great pleasure to know that IMA Academy of Medical Specialities is organizing its Annual National Conference on 19th & 20th December 2021.

IMA Academy of Medical Specialities was formed in the year 1979 by the visionaries of Indian Medical Association with the intention of providing a forum for Specialists of all branches of medicine to discuss academic matters of multi-disciplinary interest. It has motivated specialists to actively participate in all the activities of the Indian Medical Association.

I take this opportunity to invite all the leaders and members of IMA AMS wing to attend IMA NATCON 2021 which is going to be held at Patna on 27th & 28th December, 2021. We wish to welcome maximum number of delegates from your wing.

I wish that this IMA AMS Conference will be a grand success.

Dr. Sahajanand Prasad Singh
National President Elect, IMA

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Message



Dr. Jayesh M. Lele
Hony. Secretary General
IMA Hqrs

Warm Greetings from Indian Medical Association (HQs.)!

I am delighted to know that IMA Academy of Medical Specialties is releasing an E-version of the prestigious Annual "Annals" during the Annual National Conference of IMA & IMA AMS Andhra Pradesh State under the auspices of IMA AMS HQs on 19th & 20th December 2021 at Tirupati.

Such publications, besides giving an insight into activities of this important wing, also spreads awareness and information about the latest trends and standards of advanced treatments in different fields of specialized medicine.

I hope the deliberations at the Annual Conference will help the delegates in updating their knowledge and sharing their experiences for the benefit of people.

IMA AMS is the only platform where all specialists meet with each other and can deliberate on issues which are relevant in providing holistic treatment to patients by discussing interdisciplinary management for better outcome.

I am confident that the same will be a document of study and reference for our members. I convey my best wishes to the Advisory Board of Annals and I hope it would provide useful material to its members.

I wish the IMA AMSCON 2021 a tremendous success.

Long Live IMA!!

Dr. Jayesh Lele
Hony. Secretary General

Message



Dr Ravi Wankhedkar
Past National President, IMA
Treasurer, WMA

To

TEAM IMA AMS

Festival Greetings from World Medical Association.

Hearty Congratulations to TEAM IMA AMS ably led by Dr. Shreehari Rao Gharu & Dr. Sanjeev singh Yadav for continuing the great tradition of bringing out Annals of AMS.

This edition of Annals is an excellent masterpiece as it contains scholarly articles and write-ups on the most important current health issue ,ie, Covid 19.

AMS is progressing under your leadership very well and I am also very happy to note that your team has streamlined the functioning and constitution of AMS.

I also like to congratulate and thank Team IMA Tirupati for organizing the National AMSCON under the leadership of Dr D Shreehari Rao gharu .

Tirupati is a divine destination and houses our IMA Guest house there built by the untiring efforts of Dr N Apparao sir .

Wishing AMSCON 2021 I grand success.

Regards

Dr Ravi Wankhedkar

Message



Dr. Daggumati Shreehari Rao
Chairman, IMA AMS HQ.

I am overwhelmed and very much honoured as a Chairman of IMA AMS HQ. During my tenure IMA AMS doing vibrant activities of membership enrollment, conducting webinars, CME's, organizing zonal conferences, conducting different courses, honouring AMS members with Professorships, Honourary fellowship, awarding Fellowship to life members of IMA AMS.

Medical profession needs regular updating of knowledge and acquainting with the latest technologies and techniques. IMA AMS is the main pillar of the academic wings of IMA. Annals can help the medical profession with many interesting articles, is useful for researchers; it's an official record of the events that happened in the year.

I am sure, the e-version of annals will benefit to the modern medical profession and professionals during this digital era.

It gives me immense pleasure to invite you all for IMA AMS NATCON 2021 at the holy, mighty place and temple city of Tirupathi an 19th & 20th December 2021.

I believe that this National Conference shall infuse confidence in all of us and precise inputs and sharing of experiences by the experts will spread knowledge and wisdom. Our National IMA leaders will throw light on various problems faced by our professional colleagues.

I congratulate and thank IMA AMS HQ team for their commitment and dedication towards the academic activities.

Thank you

Long live IMA

Dr. Daggumati Shreehari Rao
Chairman, IMA AMS HQ.

Message



Dr. G. N. Prabhakara

Chairman Elect
IMA AMS -2021-2022

Dear IMA Thirupathi and IMA AMS Thirupathi

I am overwhelmed to see the activeness of your branch. You have accepted a challenge to conduct a prestigious national IMA AMS conference in a very short period. I must congratulate the organisers and my brother Dr. D. Shreehari Rao for a brave decision. Under the active guidance of our Secretary Dr. Sanjeev Singh Yadav, the conference will be meaningful. Hope all the delegates will enjoy the hospitality, divine darshan and a feast of knowledge and the awards and Fellowships. Once again I wish all the best and a grand success of the conference.

Dr. G. N. Prabhakara

Chairman Elect
IMA AMS -2021-2022

Message



Dr. Surya Kant
National Vice Chairman
IMA-AMS

Indian medical association is an autonomous and voluntary body and the largest Medical professional Association of world with a membership of about 4 lakhs Doctors of Modern medicine, that works across the country for the safekeeping of the community and fraternity. It is actively involved in spreading medical education pertaining to all domains of medical science. The credits of the dynamic functioning of the activities of the Indian Medical association goes to the co-ordinated efforts of the office bearers at all levels of the Association.

IMA AMSCON 2021, the Annual National Conference of Indian Medical Association Academy of Medical Specialties (IMA-AMS) is being organized by IMA & IMA AMS Andhra Pradesh (AP) State under the auspices of IMA AMS Head Office on 27th & 28th November 2021 at Tirupati. I am happy that after successfully combating the COVID crisis by our fraternity, now this conference is being organized on Hybrid mode and that is combination of Physical and Virtual platforms.

I sincerely congratulate to the organizers of IMA AMSCON 2021 for the grand success of the conference and may it be a splendid event, both in terms of intellectual quality and social gratification.

I am sure the conference will be a scientific feast which will enlighten our members and will be cherished for long.

Dr. Surya Kant
National Vice Chairman IMA-AMS

Message



Dr. Kiranshankar Wasudeo Deoras

Past Chairman,
IMA AMS Hqrs

To

Dr. Sanjeev Singh Yadav ji
Hony. Secretary IMAAMS
National Headquarters Hyderabad.

Dear sir,

Warm greetings from Chhattisgarh on the eve of Dev jagran Kartik ekadashi.
Pray lord Venkteshwar to bless us to serve needy.

I am happy to note that IMAAMS is publishing the E-Version of prestigious annual "Annals" which was published regularly and efforts of learned faculties helped fraternity to be in touch with recent updates . During Covid -19 period your able leadership , constant supervisory skills had organized many CME on virtual platform and I have full confidence that during this corona free period you will organize more CME activities with vigor and vitality in all zones. a part of our IMA prayer

सर्वे भवन्तु सुखिनः,
सर्वे सन्तु निरामयाः।
सर्वे भद्राणि पश्यन्तु ,
मां कश्चित् दुख भाग भवेत् ॥

May everyone be happy,
May everyone be healthy,
May everyone see happening good ,
No one shall have sorrow.

My all best wishes for this publication and forthcoming IMA AMSCON 2021.

Thanking you,

Dr. Kiranshankar Wasudeo Deoras

Past Chairman IMA AMS Hqrs

Message



Prof. Dr. A. Zameer Pasha
President - IAGES (2017-18)

Dear Dr. Sanjeev Singh Yadav,

IAM-AMS Greetings!

Delighted that IMA AMSCON - 2021 is being organized by IMA AMS AP State and is being held on 19th & 20th December 2021 at Tirupati.

IMA AMS the specialist academic wing of IMA is doing yeoman service to the multifarious specialities.

Doubtlessly IMA is the mother of all specialities Associations. Am certain that you and your dynamic team will leave no stone unturned to make this academic bonanza a meteoric success.

With Best Wishes and Regards,

Yours in IMA,

Prof.Dr.A.Zameer Pasha
Past Chairman, IMA - AMS (Hqrs)

Message



Dr.Ajoy Kumar. Singh

Past National Chairman IMAAMS,
Past National Vice President IMA

Dear Dr. Sanjeev Singh Yadav,

Greetings and best wishes from Ranchi, Jharkhand, I am feeling honoured and privileged in sending my best wishes for the release of long awaited E version of annual "Annals" of IMA AMS, besides the physical IMA AMSCON 2021 after long painful Covid era.

I am continuously following and at times attending the IMA AMS recent activities under your dynamic Secretaryship, with guarding umbrella of Chairman Dr. D. Shree Hari Rao and with the assistance of your Hyderabad HQ dedicated team. These are simply superb.

I am sure the forthcoming conference at pious city of Tirupati, with the blessings of lord Balaji will be a grand success. I may not be there but my mind and soul will be with you all during the educational and clinical idea exchange activities, beside fellowship, prestigious convocation and it's glorious and glamorous procession which is IMA AMS specific.

While writing these words nostalgia has come back to me, for the days I spent with IMA AMS, as it's State Secretary & National Chairman, besides it's proud fellow for approximately 25 years plus.

With best wishes and all my optimistic feelings wishing you and team a grand success.

Thanking you,

Yours truly

Dr.Ajoy Kumar. Singh

M. B. B. S (Hons); M. S.(Surg); M.Ch. (Plastic surg.);
FIAMS (Plastic surg); FAIS
Past National Chairman IMAAMS,
Past National Vice President IMA
Founder Secretary IMA Jharkhand

Message



Dr. Madhuchanda Kar

Past Chairman
IMA AMS Hqrs

Dear Colleagues,

It gives me great pride and immense pleasure that the Annual National Conference of IMA-IMA-AMSCON will be held on 19th & 20th December 2021 at the holy place of Tirupati. I congratulate the organizing committee of IMA (AP) for this great endeavor. While we doctors are giving tough resistance to the COVID pandemic such meeting will definitely boost the morale of the doctors of IMA. I am sure, all of us will be really enriched with the deliberations which have been long awaited. I convey tons of best wishes to the Organizing team and I am sure it will be a grand success in the PAVITRA temple place of Tirupati. It is tough going in this pandemic but enthusiasm amongst IMA members for such physical meeting has reached new heights. Wish all my colleagues of IMA-AMS safe and healthy life ahead. As frontline Covid warriors we all look forward to watch such galaxy of IMA leaders who will show us the way forward.

Jai Hind

Long Live IMA

Dr. Madhuchanda Kar

Past Chairman
IMA AMS Head Quarters

Message



Dr. Natwar Sharda

Dean IMA CGP Hqrs
Past Chairman IMA AMS Hqrs

Namaskar,

It is a matter of pride and conviction that IMA Academy of Medical Specialities is coming up with its conference and a souvenir and I convey all my good wishes to the organising team and expect a scientific treat will be served for the benefit of mankind and the society at large.

It is true that medical fraternity has to keep abreast with all modern developments at machine and electronics level and so a man behind the machine has to keep always updated and upgraded of their Super Speciality skill in particular.

Academy of Medical Specialities has been flag bearer of keeping the doctors updated with recent developments in the field of medicine and surgery and it is the duty of the member doctors to keep spreading the message among non-members also that Academy is working for skill development and one has to take care of his or her skills to be updated regularly.

Wishing you again a very bright and successful event on this conference.

Thanking you

Dr. Natwar Sharda

Dean IMA CGP Hqrs, Chennai
Past Chairman IMA AMS Hqrs, Hyderabad

Message



Dr. M. S. Ashraf

Past Chairman IMA AMS 2020

It gives me immense pleasure to be part of the IMA AMSCON 2021 to be held at Tirupathi.

The annals to be published as an E-version will benefit our members and delegates. I am confident the articles by renowned teachers on various topics will be useful to one and all.

I wish the conference all success.

Thanking you

Dr. M. S. Ashraf

Past Chairman IMA AMS 2020

Message



Dr. M. S. Hari Babu
Past Secretary IMA AMS Hqrs

I am glad to know that IMA AMS National AMSCON-2021 will be held on 19th & 20th December 2021, Hotel Fortune Select Grand Ridge, at Tirupati, Andhra Pradesh.

It is a herculean task to organize this conference especially when the Covid Pandemic is still active, so everyone should take Covid related precautions.

This conference gives an opportunity to meet and greet old friends and make new ones.

I Congratulate the National Chairman IMA AMS & Organising Chairman Dr. D. Shreehari Rao and his dedicated team.

I also congratulate Dr. Sanjeev Singh Yadav, Hon. National Secretary IMA AMS Hqrs, Hyderabad

My best wishes to make this conference great success and memorable one.

Dr. M. S. Hari Babu
Past Secretary IMA AMS Hqrs (2011-2012)

Message



Dr E Prabhavathi
Past Secretary IMA AMS Hqrs

First of all, I would like to congratulate the organizers of E - Version of the prestigious Annual "Annals" organised by IMA AMS Hqrs Hyderabad & IMA AMSCON 2021 at Tirupati and wish them Grand success for this conference. Since the past few years, entire medical fraternity has been going through the turbulences of NMC, Mixopathy and violence on doctors, none the less, rising suicide. Still AMS continues to strive for academic upgradation by bringing in many fellowships especially in infertility and endoscopy and many others, reaching out to help updating the practitioners.

The recent pandemic has demanded rapid changes in investigation and treatment protocols in all the specialties. Seeing the recent trends, we should always be updated to give best care to our patients following protocols endorsed by the concerned authorities.

AMS continues to spread the academic knowledge even at these hectic times of pandemic reaching out to our medical fraternity with latest updates and preventive measures. I'm happy that IMA AMS now brings these latest updates to your laptop in a novel way through E version of the Prestigious Annual Annals; which you can learn from comfort of your own home. I hope you enjoy this academic feast.

Dr E Prabhavathi
Past Secretary IMA AMS Hqrs (2013-2014)

Message



Dr. Pulla Rao

Past Secretary IMA AMS Hqrs
Past Dean of IMA CGP Hqrs

It gives me immense pleasure the IMA AMS Hqrs in coming out Souvenir. AMS is asset to IMA and plays a major role in E-Version. Even though entire IMA is busy with turbulences of NMC, Mixopathy and violence on doctors are committing suicide. Still AMS continues to strive for academic up gradation.

AMS Started infertility, Laparoscopy, Endoscopy and many other speciality Courses.

This conference is helpful to know not only the updated scientific medical practices but also thought processes behind the decisions that each medical professional makes.

I must thank organizing Chairman Dr. D. Shreehari Rao and other members of Organising Committee for conducting AMSCON-2021 on 19th & 20th December 2021 at Tirupati.

I wish the conference will be a grand success with a good message to Doctors.

Dr. Pulla Rao

Past Secretary IMA AMS Hqrs
Past Dean of IMA CGP Hqrs

Message



Dr. V.S. Rao

Past Secretary
IMA AMS Hqrs

I am very happy to note that Annual National Conference of IMA Academy of Medical Specialities "IMA AMS NATCON-2021, Tirupati is being Organized on 19th & 20th December 2021.

I am delighted to note that IMA AMS (Hqrs) is publishing the "Prestigious Annals" during the above conference.

Such deliberations in the fields of medicine helps the members to meet, exchange their views update their knowledge and expertise on the latest trends in the medical field and medical technology for better and improved patient care besides improving their personal relationships.

I also convey my best wishes to all the delegates and hope that each one of them will feel empowered and cherish the memories of the conference.

I take this opportunity to congratulate the organizers of the Conference and wish them a grand success.

Long Live IMA & AMS

Dr. V. S. Rao

Past Secretary IMA AMS Hqrs

Message



Dr. Mohan Gupta

Past Secretary
IMA AMS Hqrs

Dear Friends,

It gives me immense pleasure to write a message for IMA AMSCON - 2021 being held in the beautiful and religious city of Tirupati. As the Immediate Past National Secretary, IMA AMS Headquarters, I can fully understand the academic importance of the IMA Academy of Medical Specialities and its annual conference. I have gone through the scientific program and could see its rich qualitative academic content. I can also envisage the programme's great potential to discuss and learn the art and science of medicine and support and encourage the sharing of information among participating medical specialists.

I wish you all much success with the Conference and hope that new perspectives are gained by all who participate in the meeting.

Dr. Mohan Gupta

Past Secretary IMA AMS Hqrs

Message



Dr. E. Ravindra Reddy

Chairman Medical Council, Telangana State
National Vice President, IMA Hqrs -2021-2022

I am delighted to note that IMA AP State Branch under the auspices of IMA AMS Head Office is organizing IMA National "AMSCON-2021" on 19th & 20th December 2021 at Hotel fortune Select Grand Ridge, Tirupati.

IMA AMS is doing a great job by releasing these Annals. I am sure this will enhance the knowledge and expertise of our members in the latest advancements in medicine and medical technology.

I hope that this Conference will bring together research workers, academicians and practicing young doctors to a common platform so as to exchange ideas and stimulate discussion on current problems and develop strategies in the field of monitoring the performance of medical system. The deliberations at the conference will enhance the knowledge and expertise of the participants on latest advancements in medicine and medical technology.

CME is most essential for Medical practitioners as it keep them in touch with modern and latest treatment and diagnostic techniques in various medical fields. IMA has been promoting CME and conducting CME programmes for the last several decades and can look back with satisfaction and pride at this achievement. I am sure; participants will find the CME Programme highly enriching and beneficial.

My best wishes to Dr. D. Shreehari Rao, Chairman AMS Hqrs Dr. Sanjeev Singh Yadav and the organizing team for great success of the conference.

Long Live IMA!

Dr. E. Ravindra Reddy

Chairman Medical Council, Telangana State
National Vice President, IMA Hqrs -2021-2022

From Secretary's Desk



Dr. Sanjeev Singh Yadav

National Secretary
IMA AMS

I am really honored as Secretary IMA AMS to communicate with you through these Annals. IMA Academy of Medical Specialities was established in the year 1979 with the following objectives:

- To provide a forum to Specialists and Super-specialties of all branches of Medicine to discuss multi-disciplinary matters of academic interest
- To promote and encourage unity among the members of IMA
- To enhance image of IMA
- To increase Life Membership and Fellowship of IMA AMS
- To update all the members of IMA of the recent advances in the field of Medicine and allied subjects
- To conduct C.M.Es all over India
- To conduct various Specialty and sub-specialty courses

Currently there are 19 State Chapters and 194 Branch Chapters of IMA AMS with 15933 Life Members and 2510 Fellows as on the date.

The main Activities of IMA AMS during this financial year are as under.

1. Inspected two infertility center's one is MOM IVF Centre and second one is ZIVA Fertility Centre in Hyderabad on 26th & 27th Feb 2021, satisfied with their requirements for conducting Infertility Course and permission granted by IMA AMS Head Office to Conduct Fellowship Certificate Course in Infertility of above centers.
2. We have conducted Governing Council Meeting held on 18th April 2021 be Virtual way, the meeting was presided over by Dr. Sanjeev Singh Yadav, National Secretary IMA AMS, National President IMA HQs, Dr. J. A. Jayalal and chaired by Dr. D. Shree Hari Rao, National Chairman IMA AMS and Other Governing Council members of IMA AMS from all over India are attended this meeting. The main agenda of conducting of meeting is how to improve our Membership, Courses of IMA AMS, Regional and Zonal Conferences of North, South, East, West and central hosting by IMA AMS, AMSCON-2021, and Fellowships & Professorship of IMA AMS.

3. We IMA AMS Hqrs Released Press Note against to Yoga guru Ramdev on 7th June 2021, over his alleged Statements against allopathy, even as the his firm Patanjali issued a clarification saying he has no ill-will against modern science or its Practitioners.
4. We IMA AMS Hqrs conducted a live webinar on " COVID-19 Reinfections after Vaccination: Management & Treatment" on 9th June 2021 at 6:30 to 8:30 PM. Inauguration by Dr. J. A. Jayalal, National President IMA, welcome note by Dr. D. Shree Hari Rao, National Chairman IMA AMS. Nearly 400 to 500 members are registered. **Session 1:** Covid -19 Reinfections after Vaccination by Dr. Prof. Pradyut Waghray, Prof & HOD, SVS Medical College. Mahbubnagar, Sr. Consultant Pulmonologist, Apollo Hospitals, Hyderabad, Managing Director of Kunal Institute of Medical Specialties Pvt Ltd. **Session:2:** Management & Treatment of Covid -19 after vaccination by Dr. M. S. Mukarjee, MD, DM, DNB, FESC, Senior Interventional Cardiologist, Medicover Hospitals, Director, Pulse Heart Center, Founder-Ex-President, IMA Kukatpally.
5. We IMA AMS Hqrs Released Press Note on 17th June 2021. The cause of Central Law violence against Non-viable healthcare professionals and assault on Doctors, with the slogan of "Save the Saviours".
6. We IMA AMS Hqrs successfully Launched "**IMA AMS UPDATED WEBSITE**", inaugurated by Dr. J. A. Jayalal, National President IMA along with Dr. Jayesh M. Lele, Hon. Secretary General IMA, Dr. D. Shree Hari Rao, National Chairman AMS, Dr. G. N. Prabhakara, Elect Chairman AMS, Dr. Ravi Wankhedkar, Past National President IMA, Dr. K. Vijay Kumar, Past National President, Dr. E. Ravinder Reddy, Elect National Vice President IMA, Dr. D. Lava Kumar Reddy, President IMA TS, National Joint Secretaries of AMS Dr. B. Narendra Reddy, Dr. G. Sampath and Hon. Editor of AMS Dr. Srirang Abkari, and other National Office Bearers and State Chairman & Secretaries of IMA AMS have participated.
7. **We IMA AMS HQrs providing free Zoom Link to conduct State/Branch webinars via IMA AMS Hqrs.**
8. NRI Institute of Medical Sciences (NRIIMS) in Association with Indian Medical Association Academy of Medical Specialities (IMA AMS) Clinical Trials and Advanced Research Certification Course inauguration on 3rd October 2021 at Visakhapatnam, inaugurated by Dr. J. A. Jayalal, National President IMA along with Dr. Jayesh M. Lele, Hon. Secretary General IMA, Dr. D. Shree Hari Rao, National Chairman AMS and IMA & AMS AP State Office Bearers.
9. We IMA AMS Hqrs have formed North East Zonal Chapter. There are 8 States in the North East region of India, which are Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Tripura and Sikkim. Assam is the only State in the North East having its own AMS State Branch. This will help the whole North East to conduct Webinars, CME and in turn the Membership growth will help the IMA to make a solid foundation for Academic and other Activities.
10. **For the first time, IMA AMS Head Quarters successfully hosted all Zonal Conferences successfully especially in this pandemic year. The details as follows:**

Zonal Conferences:

North Zone - Held on 20th & 21st Nov 2021 (Virtual Way)

- | | |
|---------------------|---|
| South Zone | - Held on 12 th September 2021 Tamil Nadu State (Virtual Way) |
| East Zone | - Held by Assam State in the month of December (Virtual Way) |
| West Zone | - Held on 10 th Oct 2021, Nashik Branch, Maharashtra State (Physical) |
| National Conference | - AMSCON-2021 on 27 th & 28 th November 2021, IMA AP State, Tirupathi.
(Physical Meeting) included 2 nd Governing Council Meeting will be held on
28 th Nov 2021 at Tirupati. |

11. IMA AMS Kerala, Haryana, Bihar, Bengal, Assam, Orissa, Tamil Nadu, Andhra Pradesh & Karnataka States are conducted webinars with Associate of Various Specialties under the IMA AMS Hqrs. Dr. D. Shreehari Rao, Chairman and Dr. Sanjeev Singh Yadav, Hon. Secretary IMA AMS Hqrs and various State Chairman & Secretaries and IMA senior leaders are participated all webinars.

I would like to congratulate our Editor (Annals) Dr. Srirang Abkari for tirelessly working day and night to bringing out these Annals.

My sincere thanks to our Chief Patron Dr. Ketan Desai, Dr. J. A. Jayalal, National President, IMA Hqrs, Dr. Sahajanand P.D. Singh, National President Elect IMA Hqrs, Dr. Jayesh M Lele, Hon. Secretary General, IMA Hqrs, Dr. Anil Goyal, Finance Secretary IMA Hqrs, Dr. D. Shree Hari Rao, National Chairman, IMA AMS Hqrs and Dr. G. N. Prabhakara, Elect Chairman IMA AMS Hqrs, Dr. Surya Kant, Vice Chairman, IMA AMS Hqrs for their valuable guidance and suggestions.

My sincere thanks to the Continues Guidance by Senior IMA luminaries in conducting the day to day affairs of AMS is always a gratitude and well wishes by our senior leaders, Dr. Ved Prakash Mishra, Dr. Ravi Wankhedkar, Dr. Vinay Agarwal, Dr. G. Samaram, Dr. S. Arulrahj, Dr. Marthanda Pillai, Dr. K. Vijay Kumar, Dr. Shantanu Sen, Dr. Rajan Shama, Dr. R. V. Asokan and all other senior IMA members.

And also thanks to Dr. B. Narendra Reddy and Dr. G. Sampath, Joint Secretaries of IMA AMS Hqrs, especially thanks to Dr. Srirang Abkari, Editor of Annals IMA AMS Hqrs for selecting a comprehensive Covid-19 detailed Annals. I also thanks to Dr. D. Nageswar Reddy, Dr. Rajeev Jayadevan, Dr. M. S. S. Mukharjee, Dr. Ashok Rai and all other contributors to the Annals.

My personal thanks to Dr. E. Ravindra Reddy, Vice-President Elect IMA Hqrs 2021-2022, and Dr. Dilip Bhanushali, Central Council Member and also thanks to Dr. V. Sadananda Rao, Past National Vice Chairman IMA AMS, Dr. D. Lavakumar Reddy, Imm. Past State President IMA TS, Dr. M. Sampath Rao, President IMA TS and Dr. B. N. Rao, President Elect -2021-2022 IMA TS for their valuable guidance and suggestions.

Long Live IMA & IMA AMS

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Dr. Srirang Abkari
Hon. Editor (Annals),
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Roll of National Chairmen & Secretaries of IMA AMS Hqrs

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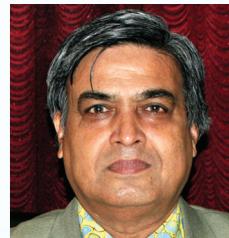
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2009-2010



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Tamil Nadu
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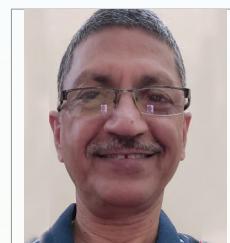
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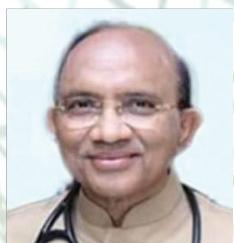
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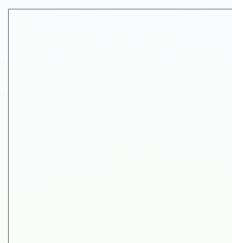
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COVID 19 - A Time Line of Events



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In what began as a non-prominent news item of some respiratory infections in China on the last day of 2020, to a most devastating pandemic which has changed all our lives, COVID-19 has been on everyone's mind for every single day for nearly 2 years now. This review aims to highlight the timeline of important events of the COVID-19 pandemic all across the world in general and in India in particular. The pandemic seems to be never ending and has not let normalcy return. May be it will be a new normal from now on. In hindsight, we can reflect on what could have been done to nip it in the bud and the opportunities lost. Nevertheless, the magnitude of the effort in rapidly establishing diagnostic, therapeutic and preventive policies for the safety of mankind is a promising lesson which will help us in better dealing with such calamities in the future.

31 Dec 2019

The World Health Organization's (WHO's) Country Office in the People's Republic of China picked up a media statement by the Wuhan Municipal Health Commission from their website on cases of 'viral pneumonia' in Wuhan, People's Republic of China.

The Country Office notified the International Health Regulations (IHR) focal point in the WHO Western Pacific Regional Office about the Wuhan Municipal Health Commission media statement of the cases and provided a translation of it.

WHO's Epidemic Intelligence from Open Sources (EIOS) platform also picked up a media report on ProMED (a programme of the International Society for Infectious Diseases) about the same cluster of cases of "pneumonia of unknown cause", in Wuhan.

1 Jan 2020

WHO requested information on the reported cluster

of atypical pneumonia cases in Wuhan from the Chinese authorities.

WHO activated its Incident Management Support Team (IMST), as part of its emergency response framework, which ensures coordination of activities and response across the three levels of WHO (Headquarters, Regional, Country) for public health emergencies.

2 Jan 2020

The WHO Representative in China wrote to the National Health Commission, offering WHO support and repeating the request for further information on the cluster of cases.

WHO informed Global Outbreak Alert and Response Network (GOARN) partners about the cluster of pneumonia cases in the People's Republic of China. GOARN partners include major public health agencies, laboratories, sister UN agencies, international organizations and NGOs.

3 Jan 2020

Chinese officials provided information to WHO on the cluster of cases of 'viral pneumonia of unknown cause' identified in Wuhan.

4 Jan 2020

WHO tweeted that there was a cluster of pneumonia cases – with no deaths – in Wuhan, Hubei province, People's Republic of China, and that investigations to identify the cause were underway.

5 Jan 2020

WHO shared detailed information about a cluster of cases of pneumonia of unknown cause through the IHR (2005) Event Information System, which is accessible to all Member States. The event notice

provided information on the cases and advised Member States to take precautions to reduce the risk of acute respiratory infections.

WHO issued its first Disease Outbreak News report. The report contained information about the number of cases and their clinical status; details about the Wuhan national authority's response measures; and WHO's risk assessment and advice on public health measures. It advised that "WHO's recommendations on public health measures and surveillance of influenza and severe acute respiratory infections still apply".

9 Jan 2020

WHO reported that Chinese authorities have determined that the outbreak is caused by a novel coronavirus.

10-12 Jan 2020

WHO published a comprehensive package of guidance documents for countries, covering topics related to the management of an outbreak of a new disease:

- Infection prevention and control
- Laboratory testing
- National capacities review tool
- Risk communication and community engagement
- Disease Commodity Package
- Disease Commodity Package
- Travel advice
- Clinical management
- Surveillance case definitions

11 Jan 2020

WHO tweeted that it had received the genetic sequences for the novel coronavirus from the People's Republic of China and expected these to soon be made publicly available.

Chinese media reported the first death from the novel coronavirus.

12 Jan 2020

WHO provides further information on the outbreak to the public based on information provided by

the National Health Commission.

13 Jan 2020

The Ministry of Public Health in Thailand reported an imported case of lab-confirmed novel coronavirus from Wuhan, the first recorded case outside of the People's Republic of China.

WHO publishes first protocol for a RT-PCR assay by a WHO partner laboratory to diagnose the novel coronavirus.

14 Jan 2020

WHO held a press briefing during which it stated that, based on experience with respiratory pathogens, the potential for human-to-human transmission in the 41 confirmed cases in the People's Republic of China existed: "it is certainly possible that there is limited human-to-human transmission".

WHO tweeted that preliminary investigations by the Chinese authorities had found "**no clear evidence of human-to-human transmission**". In its risk assessment, WHO said additional investigation was "needed to ascertain the presence of human-to-human transmission, modes of transmission, common source of exposure and the presence of asymptomatic or mildly symptomatic cases that are undetected".

15 Jan 2020

The Japanese Ministry of Health, Labour and Welfare informed WHO of a confirmed case of a novel coronavirus in a person who travelled to Wuhan. This was the second confirmed case detected outside of the People's Republic of China.

16 Jan 2020

The Pan American Health Organization/WHO Regional office for the Americas (PAHO/AMRO) issued its first epidemiological alert on the novel coronavirus. The alert included recommendations covering international travellers, infection prevention and control measures and laboratory testing.

19 Jan 2020

The WHO Western Pacific Regional Office (WHO/WPRO) tweeted that, according to the latest

information received and WHO analysis, there was evidence of limited human-to-human transmission.

20 Jan 2020

WHO published guidance on home care for patients with suspected infection.

20-21 Jan 2020

WHO conducted the first mission to Wuhan and met with public health officials to learn about the response to the cluster of cases of novel coronavirus

21 Jan 2020

WHO/WPRO tweeted that it was now very clear from the latest information that there was "at least some human-to-human transmission", and that infections among health care workers strengthened the evidence for this.

The United States of America (USA) reported its first confirmed case of the novel coronavirus. This was the first case in the WHO Region of the Americas.

22 Jan 2020

The WHO mission to Wuhan issued a statement saying that evidence suggested human-to-human transmission in Wuhan but that more investigation was needed to understand the full extent of transmission.

22-23 Jan 2020

The WHO Director-General convened an IHR Emergency Committee (EC) regarding the outbreak of novel coronavirus. The EC was charged with advising the Director-General as to whether the outbreak constituted a public health emergency of international concern (PHEIC).

The Committee was not able to reach a conclusion on 22 January based on the limited information available.

The EC met again on 23 January and members were equally divided as to whether the event constituted a PHEIC, as several members considered that there was still not enough information for it, given its restrictive and binary nature (only PHEIC or no PHEIC can be determined; there is no intermediate level of warning). As there was a divergence of views, the

EC did not advise the Director-General that the event constituted a PHEIC but said it was ready to be reconvened within 10 days.

24 Jan 2020

France informed WHO of three cases of novel coronavirus, all of whom had travelled from Wuhan. These were the first confirmed cases in the WHO European region (EURO).

The Director of the Pan American Health Organization (PAHO) urged countries in the Americas to be prepared to detect early, isolate and care for patients infected with the new coronavirus, in case of receiving travelers from countries where there was ongoing transmission of novel coronavirus cases.

26 Jan 2020

WHO released its first free online course on the novel coronavirus on its OpenWHO learning platform.

27-28 Jan 2020

A senior WHO delegation led by the Director-General arrived in Beijing to meet Chinese leaders, learn more about the response in the People's Republic of China, and to offer technical assistance. The Director-General met with President Xi Jinping on 28 January, and discussed continued collaboration on containment measures in Wuhan, public health measures in other cities and provinces, conducting further studies on the severity and transmissibility of the virus, continuing to share data, and a request for China to share biological material with WHO. They agreed that an international team of leading scientists should travel to China to better understand the context, the overall response, and exchange information and experience.

29 Jan 2020

The United Arab Emirates reported the first cases in the WHO Eastern Mediterranean Region.

30 Jan 2020

The Director-General declared the novel coronavirus outbreak a public health emergency of international concern (PHEIC), WHO's highest level of alarm.

2 Feb 2020

First dispatch of RT-PCR lab diagnostic kits shipped to WHO Regional Offices.

3 Feb 2020

WHO finalised its Strategic Preparedness and Response Plan (SPRP), centred on improving capacity to detect, prepare and respond to the outbreak.

4 Feb 2020

The WHO Director-General asked the UN Secretary-General to activate the UN crisis management policy, which held its first meeting on 11 February.

The director said "We have a window of opportunity. While 99% of cases are in China, in the rest of the world we only have 176 cases".

Responding to a question at the Executive Board, the Secretariat said, "it is possible that there may be individuals who are asymptomatic that shed virus, but we need more detailed studies around this to determine how often that is happening and if this is leading to secondary transmission".

5 Feb 2020

WHO's headquarters began holding daily media briefings on the novel coronavirus, the first time that WHO has held daily briefings by the Director-General or Executive Director of the WHO Health Emergencies Programme.

11 Feb 2020

WHO announced that the disease caused by the novel coronavirus would be named COVID-19.

Following best practices, the name of the disease was chosen to avoid inaccuracy and stigma and therefore did not refer to a geographical location, an animal, an individual or group of people

12 Feb 2020

Supplementing the SPRP with further detail, WHO published Operational Planning Guidelines to Support Country Preparedness and Response, structured around the eight pillars of country-level coordination, planning, and monitoring; risk communication and community engagement;

surveillance, rapid response teams, and case investigation; points of entry; national laboratories; infection prevention and control; case management; and operational support and logistics.

14 Feb 2020

Based on lessons learned from the H1N1 and Ebola outbreaks, WHO finalised guidelines for organizers of mass gatherings, in light of COVID-19.

15 Feb 2020

The Director-General made three requests of the international community: use the window of opportunity to intensify preparedness, adopt a whole-of-government approach and be guided by solidarity, not stigma. He also expressed concern at the global lack of urgency in funding the response.

16 Feb 2020

The WHO-China Joint Mission began its work. As part of the mission to assess the seriousness of this new disease; its transmission dynamics; and the nature and impact of China's control measures, teams made field visits to Beijing, Guangdong, Sichuan and Wuhan.

19 Feb 2020

Weekly WHO Member State Briefings on COVID-19 began, to share the latest knowledge and insights on COVID-19.

24 Feb 2020

The Team Leaders of the WHO-China Joint Mission on COVID-19 held a press conference to report on the main findings of the mission.

The Mission warned that "much of the global community is not yet ready, in mindset and materially, to implement the measures that have been employed to contain COVID-19 in China".

The Mission stressed that "to reduce COVID-19 illness and death, near-term readiness planning must embrace the large-scale implementation of high-quality, non-pharmaceutical public health measures", such as case detection and isolation, contact tracing and monitoring/quarantining and community engagement.

In addition to the Mission press conference, WHO published operational considerations for managing COVID-19 cases and outbreaks on board ships, following the outbreak of COVID-19 during an international voyage.

25 Feb 2020

Confirmation of the second case in WHO's African Region, in Algeria. This followed the earlier reporting of a case in Egypt, the first on the African continent.

27 Feb 2020

WHO published guidance on the rational use of personal protective equipment, in view of global shortages. This provided recommendations on the type of personal protective equipment to use depending on the setting, personnel and type of activity.

28 Feb 2020

The Report of the WHO-China Joint Mission was issued, as a reference point for countries on measures needed to contain COVID-19.

29 Feb 2020

WHO published considerations for the quarantine of individuals in the context of containment for COVID-19. This described who should be quarantined and the minimum conditions for quarantine to avoid the risk of further transmission.

6 Mar 2020

WHO published the Global Research Roadmap for the novel coronavirus developed by the working groups of the Research Forum.

The Roadmap outlines key research priorities in nine key areas. These include the natural history of the virus, epidemiology, diagnostics, clinical management, ethical considerations and social sciences, as well as longer-term goals for therapeutics and vaccines.

7 Mar 2020

To mark the number of confirmed COVID-19 cases surpassing 100 000 globally, WHO issued a statement calling for action to stop, contain, control, delay and reduce the impact of the virus at every opportunity.

10 Mar 2020

WHO, UNICEF and the International Federation of Red Cross and Red Crescent Societies (IFRC) issued guidance outlining critical considerations and practical checklists to keep schools safe, with tips for parents and caregivers, as well as children and students themselves.

11 Mar 2020

Deeply concerned both by the alarming levels of spread and severity, and by the alarming levels of inaction, WHO made the assessment that COVID-19 could be **characterized as a pandemic**.

13 Mar 2020

The Director-General said that Europe had become the epicentre of the pandemic with more reported cases and deaths than the rest of the world combined, apart from the People's Republic of China.

13 Mar 2020

WHO, the UN Foundation and partners launched the COVID-19 Solidarity Response Fund to receive donations from private individuals, corporations and institutions. In just 10 days, the Fund raised more than US\$70 million, from more than 187,000 individuals and organizations, to help health workers on the front lines to do their life-saving work, treat patients and advance research for treatments and vaccines.

16 Mar 2020

WHO launched the COVID-19 Partners Platform as an enabling tool for all countries, implementing partners, donors and contributors to collaborate in the global COVID-19 response. The Partners Platform features real-time tracking to support the planning, implementation and resourcing of country preparedness and response activities.

18 Mar 2020

WHO and partners launched the Solidarity trial, an international clinical trial that aims to generate robust data from around the world to find the most effective treatments for COVID-19

18 Mar 2020

WHO published guidance on mental health and psychosocial considerations during the COVID-19 outbreak.

20 Mar 2020

WHO Health Alert, which offers instant and accurate information about COVID-19, launched on WhatsApp. It is available in multiple languages with users around the world.

21 Mar 2020

In light of many Member States facing shortfalls in testing capacity, WHO published laboratory testing strategy recommendations for COVID-19.

23 Mar 2020

WHO and FIFA launched the 'Pass the message to kick out coronavirus' awareness campaign, led by world-renowned footballers, who called on people around the world to protect their health, through hand washing, coughing etiquette, not touching one's face, maintaining physical distance and staying home if feeling unwell.

28 Mar 2020

With many health facilities around the world overwhelmed by the influx of COVID-19 patients seeking medical care, WHO published a manual on how to set up and manage a severe acute respiratory infection treatment centre and a severe acute respiratory infection screening facility in health care facilities to optimise patient care.

31 Mar 2020

WHO published a Scientific Brief on the off-label use of medicines for COVID-19, addressing the issue of compassionate use. WHO announced the launch of a chatbot with Rakuten Viber, a free messaging and calling app. Subscribers to the WHO Viber chatbot receive notifications with the latest news and information directly from WHO. It is available in multiple languages with users around the world.

2 Apr 2020

WHO reported on evidence of transmission from symptomatic, pre-symptomatic and asymptomatic people infected with COVID-19, noting that

transmission from a pre-symptomatic case can occur before symptom onset.

4 Apr 2020

WHO reported that over 1 million cases of COVID-19 had been confirmed worldwide, a more than tenfold increase in less than a month.

6 Apr 2020

WHO issued updated guidance on masks, including a new section on advice to decision-makers on mask use by healthy people in communities.

7 Apr 2020

World Health Day focused on celebrating the work of nurses and midwives at the forefront of the COVID-19 response.

9 Apr 2020

WHO marked 100 days since the first cases of 'pneumonia with unknown cause' were reported with an overview of key events and efforts taken to stop the spread of coronavirus.

11 Apr 2020

WHO published a draft landscape of COVID-19 candidate vaccines, on the basis of a systematic assessment of candidates from around the world, which continues to be updated.

15 Apr 2020

WHO finalised guidance on public health advice for social and religious practices during Ramadan, in the context of COVID-19

16 Apr 2020

WHO issued guidance on considerations in adjusting public health and social measures, such as large-scale movement restrictions, commonly referred to as '**lockdowns**'.

18 Apr 2020

WHO and Global Citizen co-hosted the 'One World: Together At Home' concert, a global on-air special to celebrate and support front line healthcare workers. The concert raised a total of \$127.9 million, providing \$55.1 million to the COVID-19 Solidarity

Response Fund and \$72.8 million to local and regional responders.

20 Apr 2020

The UN General Assembly adopted a resolution entitled '**International cooperation to ensure global access to medicines, vaccines and medical equipment to face COVID-19**'.

24 Apr 2020

WHO issued a Scientific Brief on 'immunity passports' in the context of COVID-19. This brief highlighted that there was not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an 'immunity passport' or 'risk-free certificate' and that the use of such certificates may therefore increase the risks of continued transmission.

10 May 2020

Building on previous guidance on the investigation of cases and clusters, WHO issued interim guidance on contact tracing.

15 May 2020

WHO released a Scientific Brief on multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.

18-19 May 2020

The 73rd World Health Assembly, the first ever to be held virtually, adopted a landmark resolution to bring the world together to fight the COVID-19 pandemic, co-sponsored by more than 130 countries – the largest number on record – and adopted by consensus.

The resolution calls for the intensification of efforts to control the pandemic, and "recognizes the role of extensive immunization against COVID-19 as a global public good for health", and calls for equitable access to and fair distribution of all essential health technologies and products to combat the virus.

27 May 2020

WHO published interim guidance on the clinical management of COVID-19.

29 May 2020

Thirty countries and multiple international partners and institutions launched the COVID-19 Technology Access Pool (C-TAP), an initiative to make vaccines, tests, treatments and other health technologies to fight COVID-19 accessible to all. Voluntary and based on social solidarity, C-TAP aims to provide a one-stop shop for equitably sharing scientific knowledge, data and intellectual property.

5 Jun 2020

WHO published updated guidance on the use of masks for the control of COVID-19, which provided updated advice on who should wear a mask, when it should be worn and what it should be made of.

13 Jun 2020

WHO reported that Chinese authorities had provided information on a cluster of COVID-19 cases in Beijing, People's Republic of China.

16 Jun 2020

WHO welcomed initial clinical trial results from the UK that showed dexamethasone, a corticosteroid, could be lifesaving for patients critically ill with COVID-19.

17 Jun 2020

WHO announced that the hydroxychloroquine arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped. The decision was based on large scale randomized evidence from the Solidarity, Discovery and Recovery trials, as well as a review of available published evidence from other sources, which showed that hydroxychloroquine did not reduce mortality for hospitalised COVID-19 patients.

26 Jun 2020

As part of WHO's SARS-CoV-2 global laboratory network, which has monitored virus mutations from the start of the pandemic, a specific working group on virus evolution held its first meeting.

29 Jun 2020

WHO's first infodemiology conference began, as part of the organization's work on new evidence-

based measures and practices to prevent, detect and respond to mis- and disinformation. 'Infodemiology' is the science of managing 'infodemics': the overabundance of information – some accurate and some not – occurring during an epidemic.

4 Jul 2020

WHO announced that the hydroxychloroquine and lopinavir/ritonavir arms of the Solidarity trial to find an effective COVID-19 treatment were being discontinued, building on the decision to stop the hydroxychloroquine arm on 17 June 2020

9 Jul 2020

WHO issued an updated Scientific Brief on COVID-19 transmission, providing information on how, when and in which settings the virus spreads between people. The brief described possible modes of transmission, including contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal-to-human transmission.

10 Jul 2020

To develop the scope and terms of reference for a WHO-led international mission, WHO

experts departed for China to work together with their Chinese counterparts to prepare scientific plans for identifying the zoonotic source of COVID-19. The mission objective is to advance the understanding of animal hosts for COVID-19 and ascertain how the disease jumped between animals and humans.

13 Jul 2020

The 2020 edition of the UN's 'State of Food Security and Nutrition in the World' is published, which forecasted that the COVID-19 pandemic could tip over 130 million more people into chronic hunger by the end of the year.

15 Jul 2020

The COVAX Facility, a mechanism designed to guarantee rapid, fair and equitable access to COVID-19 vaccines worldwide, secured engagement from more than 150 countries, representing over 60% of the world's population.

5 Aug 2020

The Director-General launched the #WearAMask challenge on social media to help spread the word about how and when to use a mask to protect against COVID-19. This campaign, involving a wide range of partners, is part of WHO's wider call to take a comprehensive "do it all" response to the pandemic.

7 Aug 2020

WHO published updated guidance on public health surveillance for COVID-19, which includes revised suspected and probable case definitions that integrate new knowledge about the clinical spectrum of COVID-19 and its transmission.

12 Aug 2020

WHO published updated guidance on home care for patients with suspected or confirmed COVID-19 and management of their contacts.

19 Aug 2020

On World Humanitarian Day, WHO joined with UN partners to pay tribute to the frontline workers around the world responding to COVID-19 and other health emergencies.

21 Aug 2020

WHO, in collaboration with UNICEF, published guidance on the use of masks for children in the community in the context of COVID-19.

28 Aug 2020

WHO launched its 'Science in 5' video and podcast series, featuring WHO experts giving explanations of the science on specific issues related to COVID-19, to help audiences protect themselves and others.

In the first episode, WHO's Chief Scientist explained the concept of 'herd immunity', whereby a population can be protected from a virus if a threshold of vaccination is reached.

2 Sep 2020

WHO published guidance on the role of corticosteroids in treating COVID-19, developed in collaboration with the non-profit Magic Evidence Ecosystem Foundation (MAGIC).

11 Sep 2020

WHO published interim guidance, highlighting the

value of antigen based rapid diagnostic tests for the SARS-CoV-2 virus, in areas where community transmission is widespread and where nucleic acid amplification-based diagnostic testing is either unavailable or where test results are significantly delayed.

22 Sep 2020

WHO issued the first Emergency Use Listing for a quality antigen based rapid diagnostic test for detecting the SARS-CoV-2 virus, which causes COVID-19.

1 Oct 2020

WHO published a call for expressions of interest for manufacturers of COVID-19 vaccines – to apply for approval for prequalification and/or Emergency Use Listing.

15 Oct 2020

WHO announced conclusive evidence on the effectiveness of repurposed drugs for COVID-19. Interim results from the Solidarity Trial indicated that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients.

22 Oct 2020

WHO and the Wikimedia Foundation – the nonprofit that administers Wikipedia – announced a collaboration to expand the public's access to the latest and most reliable information about COVID-19.

5 Nov 2020

WHO published terms of reference for the WHO-convened Global Study of the Origins of SARS-CoV-2. It outlines two phases of studies: Short term studies (Phase 1) will be conducted to better understand how the virus might have started circulating in Wuhan, People's Republic of China. Building on the findings of these short-term studies, and the scientific literature, longer term studies will be developed (Phase 2).

6 Nov 2020

WHO issued a Disease Outbreak News report on the SARS-CoV-2 mink-associated variant strain in Denmark. The report included an overview of the Danish public health response, and WHO risk

assessment and advice.

10 Nov 2020

WHO launched the 'We Are #InThisTogether' campaign to promote collaboration and adherence to five key measures to counter COVID-19: cleaning hands, wearing masks, coughing and sneezing safely, keeping distant and opening windows.

16 Nov 2020

The 147th session of the Executive Board resumed. In his opening remarks, the Director-General welcomed encouraging news about vaccines but emphasised that "a vaccine on its own will not end the pandemic" and other public health measures would need to continue as there was "still a long road to travel".

19th November 2020:

U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the drug baricitinib, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

20 Nov 2020

WHO published a guideline on therapeutics and COVID-19, with new information for clinicians including a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity.

3 Dec 2020

WHO issued a second Disease Outbreak News report on a SARS-CoV-2 mink-associated variant strain, reported by Danish authorities.

4 Dec 2020

Researchers in South Africa presented preliminary findings of a new recently identified variant called 501Y.V2 to the WHO Virus Evolution Working Group, which is part of the WHO SARS-CoV-2 global laboratory network.

14 Dec 2020

United Kingdom authorities reported a SARS-CoV-2 variant to WHO. The United Kingdom referred to

the variant as SARS-CoV-2 VOC 202012/01 (Variant of Concern, year 2020, month 12, variant 01).

18 Dec 2020

National authorities in South Africa announced the detection of a new variant of SARS-CoV-2 rapidly spreading in three provinces of South Africa. South Africa named this variant 501Y.V2, because of a N501Y mutation.

21 Dec 2020

WHO issued a Disease Outbreak News report on the SARS-CoV-2 VUI 202012/01 variant reported to WHO by UK authorities.

23 Dec 2020

WHO published 'A year without precedent' to tell the story of WHO's COVID-19 response through infographics and stories of impact from across the organization's activities and partnerships.

27 Dec 2020

The first-ever International Day of Epidemic Preparedness was held to advocate for the importance of the prevention of, preparedness for and partnership against epidemics.

31 Dec 2020

WHO issued its first emergency use validation for a COVID-19 vaccine and emphasized the need for equitable global access. The World Health Organization (WHO) today listed the Comirnaty COVID-19 mRNA vaccine for emergency use, making the Pfizer/BioNTech vaccine the first to receive emergency validation from WHO since the outbreak began a year ago.

WHO issued a Disease Outbreak News report on SARS-CoV-2 variants, covering reports from the Denmark, the United Kingdom and South Africa. It detailed the public health response, WHO risk assessment and WHO advice.

5 Jan 2021

WHO's Strategic Advisory Group of Experts on Immunization (SAGE) met to review the vaccine data for the Pfizer/BioNTech vaccine and formulate policy recommendations on how best to use it. The vaccine was the first to receive an emergency use validation from WHO for efficacy against COVID-19.

9 Jan 2021

WHO was notified by Japanese authorities of a SARS-CoV-2 variant, which was identified when whole-genome sequencing was conducted on samples from travellers from Brazil.

11 Jan 2021

The Director-General called for a collective worldwide commitment to ensure vaccination for health workers and those at high-risk in all countries gets underway in the first 100 days of 2021.

19 Jan 2021

The WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee met virtually to review available information and data on deaths reported in frail, elderly individuals who had received the Pfizer BioNTech COVID-19 vaccine. It was concluded that the reports did not suggest any unexpected or untoward increase in fatalities in frail, elderly individuals or any unusual characteristics of adverse events following administration of the vaccine.

25 Jan 2021

WHO issued interim recommendations for the use of the Moderna mRNA-1273 vaccine against COVID-19, developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 21 January 2021.

29 Jan 2021

WHO published its new Essential Diagnostics List, which includes WHO-recommended COVID-19 tests (PCR and Antigen).

2 Feb 2021

Nomenclature groups, the Virus Evolution Working Group and international experts held their first meeting to explore a mechanism to develop a standardized nomenclature for variants, which will be more easily understood and not be associated with any country or a region where viruses are initially identified.

8 Feb 2021

COVAX issued a statement on new variants of SARS-CoV-2, underscoring the importance of determining the AstraZeneca/Oxford vaccine's effectiveness when

it comes to preventing more severe illness caused by the B.1.351 variant, through additional studies.

10 Steps to Community Readiness, a tool on what countries should do to prepare communities for a COVID-19 vaccine, treatment, or new test, was published.

9 Feb 2021

The international team studying the origins of SARS-CoV-2 held a press briefing from Wuhan, China on their field visit to the city.

As part of efforts to expand knowledge on Post COVID-19 condition, and support patient care and public health interventions, WHO published its Post COVID case report form (CRF), designed to report standardized clinical data from individuals after hospital discharge or after the acute illness to examine the medium- and long-term consequences of COVID-19.

12 Feb 2021

In his opening remarks at WHO's press conference on COVID-19, the Director-General said that the mission to China to study the origins of the COVID-19 virus achieved a better understanding of the early days of the pandemic and had been a "very important scientific exercise in very difficult circumstances".

He confirmed that all hypotheses remained open and required further analysis and studies.

15 Feb 2021

WHO listed two versions of the AstraZeneca/Oxford COVID-19 vaccine for emergency use, giving the green light for these vaccines to be rolled out globally through COVAX. The vaccines are produced by AstraZeneca-SKBio (Republic of Korea) and the Serum Institute of India.

24 Feb 2021

COVAX's global rollout began, as Ghana became the first country outside India to receive COVID-19 vaccine doses shipped via COVAX.

25 Feb 2021

A WHO-led consortium, together with the Access to COVID-19 Tools (ACT) Accelerator Therapeutics pillar, announced the launch of a COVID-19 Oxygen Emergency Taskforce. Taskforce partners will work

together to measure oxygen demand, work with financing partners, and secure oxygen supplies and technical support for the worst-affected countries.

WHO published a special edition of its weekly epidemiological update, with working definitions for SARS-CoV-2 variants of interest and variants of concern and the associated actions WHO will take to support Member States, their national public health institutes and reference laboratories, along with the recommended actions Member States should take.

1 Mar 2021

WHO published its roadmap to improve and ensure good indoor ventilation in the context of COVID-19.

4 Mar 2021

Vaccination data were published on the WHO Coronavirus (COVID-19) Dashboard for the first time.

8 Mar 2021

WHO held a consultation on the use of trained dogs for screening COVID-19 cases.

12 Mar 2021

WHO listed the COVID-19 vaccine Ad26.COV2.S, developed by Janssen (Johnson & Johnson), for emergency use in all countries and for COVAX roll-out. The decision comes on the back of the European Medicines Agency (EMA) authorization, which was announced the day before.

15 Mar 2021

Living with the Times, a mental health and psychosocial support toolkit for older adults during the COVID-19 pandemic, is released.

16 Mar 2021

The COVID-19 detailed surveillance data dashboard went live. Features include stratification by age and sex, trends over time, case fatality ratios by age, testing, hospitalization, and data on health workers – all visible at country and regional levels. The dashboard provides the ability for users to conduct further analyses by country and selected time period.

17 Mar 2021

WHO issued interim recommendations for the use of the Janssen Ad26.COV2.S (COVID-19) vaccine, developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 15 March 2021.

WHO issued a statement on AstraZeneca COVID-19 vaccine safety signals. This followed some countries in the European Union temporarily suspending use of the AstraZeneca COVID-19 vaccine as a precautionary measure, based on reports of rare blood coagulation disorders in persons who had received the vaccine. At this point, WHO considered that the benefits of the AstraZeneca vaccine outweighed its risks and recommended that vaccinations continue.

19 Mar 2021

Having met virtually on 16 and 19 March 2021 to review available information and data on thromboembolic events (blood clots) and thrombocytopenia (low platelets) after vaccination with the AstraZeneca COVID-19 vaccine, the WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee issued a statement on safety signals related to the vaccine. Conclusions included that the AstraZeneca COVID-19 vaccine (including Covishield) continued to have a positive benefit-risk profile, with tremendous potential to prevent infections and reduce deaths across the world.

31 Mar 2021

WHO advised that ivermectin only be used to treat COVID-19 within clinical trials, due to the then-current evidence being inconclusive

10 Apr 2021

WHO marked the close of its 100-day challenge for vaccine equity, which saw tens of thousands of people and hundreds of organizations signing on to its declaration, directly calling on governments and manufacturers to speed up regulatory processes, boost manufacturing by sharing know-how and technology, and ensure that doses are shared equitably.

24 Nov 2021

WHO has designated B.1.1.529 which was first reported from South Africa as a variant of concern and labeled it as OMICRON.

TIME LINE IN INDIA

24 January 2020: Specimen Collection, Packaging and Transport Guidelines for 2019 Novel Coronavirus (2019-nCoV)

25th January 2020: National Guidelines for infection prevention and control in healthcare facilities

30th January 2020: The first cases of COVID-19 in India were reported in three towns of Kerala, among three Indian medical students who had returned from Wuhan, the epicenter of the pandemic

9th March 2020: ICMR strategy for covid-19 testing in India

13th March, 2020:

India was the 5th country in the world to sequence the viral genome (isolated from the first patients in Kerala) for inclusion in Global Initiative on Sharing All Influenza Data (GISAID)

17th March 2020:

Updated Guidelines on Clinical Management of COVID-19

Discharge Policy for suspected or confirmed novel corona virus cases in India

The health ministry decided to allow accredited private pathology labs to test for COVID-19

22nd March 2020: Janata Curfew

The Prime Minister asked people to express their gratitude to lakhs of people working at airports, hospitals and performing duties related to transportation and sanitation during the coronavirus outbreak. "I want that on March 22, we express our gratitude to them. At 5 pm on Sunday, we should stand on doors, balconies, windows of our homes and express our gratitude for five minutes," he said, adding that people can do so by clapping or ringing bells.

23rd March, 2020: The National Task Force for COVID-19 constituted by the ICMR recommended the use of hydroxychloroquine for the treatment of high-risk cases

Lockdowns were announced in Kerala

24th March 2020: Lockdown in the rest of the country

10th June, 2020: India's recoveries exceeded active cases for the first time.

June 2020: India approved the repurposing of generic versions of the antiviral medication favipiravir for the treatment of mild-to-moderate COVID-19 symptoms

July 2020: the Indian firm Biocon received emergency authorisation for the use of the repurposed drug Itolizumab in treatments for chronic plaque psoriasis, one of the symptoms of the disease.

Daily cases peaked mid-September with over 90,000 cases reported per-day, dropping to below 15,000 in January 2021.^[16]

16th January 2021: India began its vaccination programme on with AstraZeneca vaccine (Covishield) and the indigenous Covaxin.

March 2021: A second wave began which was much more devastating than the first, with shortages of vaccines, hospital beds, oxygen cylinders and other medical supplies in parts of the country. By late April, India led the world in new and active cases.

April 2021: The DCGI approved the Russian Sputnik V vaccine,

23rd April 2021: Cadila Healthcare received an emergency authorisation to repurpose Peginterferon alfa-2b, a medication used to treat hepatitis C, as a treatment for moderate COVID-19 in adults.

30th April 2021: India became the first country to report over 400,000 new cases in a 24-hour period

April- May 2021: Surge of COVID-19 associated Mucormycosis

8th May 2021, DCGI gave permission for emergency use of the drug 2-Deoxy-D-glucose developed by DRDO in collaboration with Dr. Reddy's Laboratories as an *adjunct or alternative therapy* for treating moderate to severe cases of COVID-19.

May 20th 2021: Central Drugs Standard Control Organisation (CDSCO) approves use of antibodies cocktail drug (Casirivimab and Imdevimab) for restricted emergency use to treat mild to moderate Covid-19 in adults and paediatric patients.

18th June 2021 Guidelines for Management of COVID-19 in Children (below 18 years)

15th July.2021: Genomic Surveillance for SARS-CoV-2 In India Indian SARS-CoV-2 Genomics Consortium (INSACOG): Updated guidelines and SOPs

August 20, 2021: The indigenously developed world's first DNA-based needle-free COVID-19 vaccine ZyCoV-D received emergency use authorisation from the drug regulator.

6th September 2021: DCGI approves Hetero's Tocilizumab for emergency use against Covid-19

12th October 2021: Bharat Biotech's Covaxin gets emergency approval for kids aged 2-18 years by the Subject Expert Committee of CDCSO

21st October 2021: National Comprehensive Guidelines for management of post-covid sequelae

21st October 2021, at 9:47 AM: According to the Co-WIN portal, India crossed 100 crore vaccination (1 billion) doses.

4th December 2021: Over 50% of adult population in India fully vaccinated

8th December 2021: The cumulative number of Covid-19 vaccine doses administered in India crossed 130 crore.

WORLD DATA ON COVID-19

(as on 8th December 2021)

TOTAL CASES	:	266,504,411
TOTAL DEATHS	:	5,268,849
TOTAL VACCINATIONS	:	8,158,815,265

INDIAN DATA ON COVID-19

(as on 09 December 2021)

Total Vaccination Doses	:	1,30,39,32,286
Total Samples Tested	:	65,19,50,127
Total Cases	:	3,46,66,241
Active cases	:	94742
Total Deaths (1.37%)	:	474111
Total Modern Medicine Doctor Deaths	:	1,492

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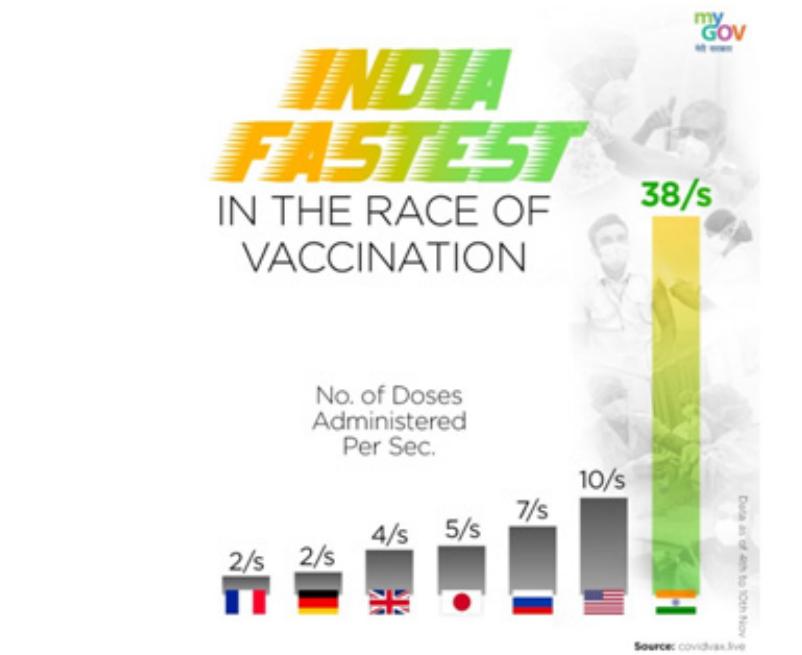


Figure1: Vaccination rate in different countries

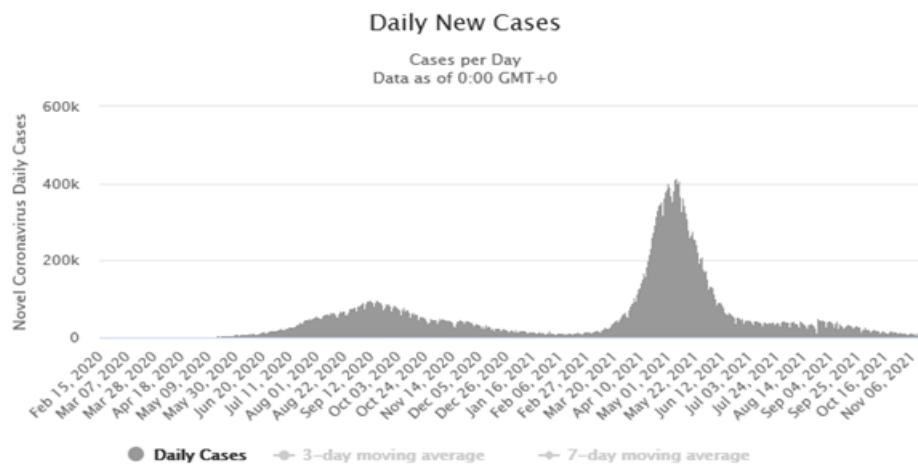


Figure 2- Daily new covid- 19 cases in India

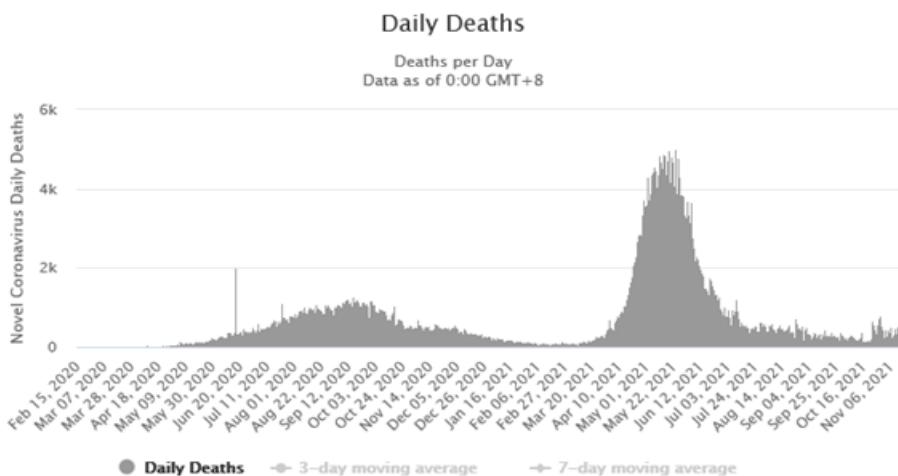


Figure 3- Daily covid-19 deaths in India

COVID 19 - An Indian Perspective

**Dr Surya Kant**

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Abstract

The COVID-19 pandemic affected millions of people across the globe. Individuals infected with the novel corona virus showed varied symptoms ranging from a mild disease to severe disease endangering life. COVID 19 has been spreading its menace since the past 2 years across the globe. India was amongst one of the most severely affected country but it was by the constant efforts of the Indian medical fraternity along with the unyielding support of the government that we were able to treat so many patients suffering from COVID and also slow further spread of the disease by propagating the fastest and largest vaccination campaign across the country. This is a matter of pride that while most of the world including few developed nations are still facing the menace of COVID 19 as 3rd and 4th waves, India has successfully contained the spread of the disease.

Key words : Covid-19, Severity, Covid appropriate behavior, Pandemic, vaccination

Introduction

An outbreak is when an illness happens in unexpected high numbers. It may stay in one area or extend more widely. An outbreak can last days or years. A **pandemic** is a disease outbreak that spreads across countries or continents. Covid 19 is one of the worst viral pandemic in the last 100 years. The origin of the virus in Wuhan city of China in early December 2019 is a mystery and most likely the route of SARS-CoV-2 emergence was from a bat lineage via an unidentified intermediate host with more frequent human contact, in which the progenitor virus might have been circulating undetected for decades. The origin and spread of the disease created a havoc and feeling of unrest in India as well, affecting nearly a population of 3.5 crore in India and more than 25 crore people globally.¹ (Table 1)

Even though the spread of the disease in the country was very unfortunate the silver lining behind its

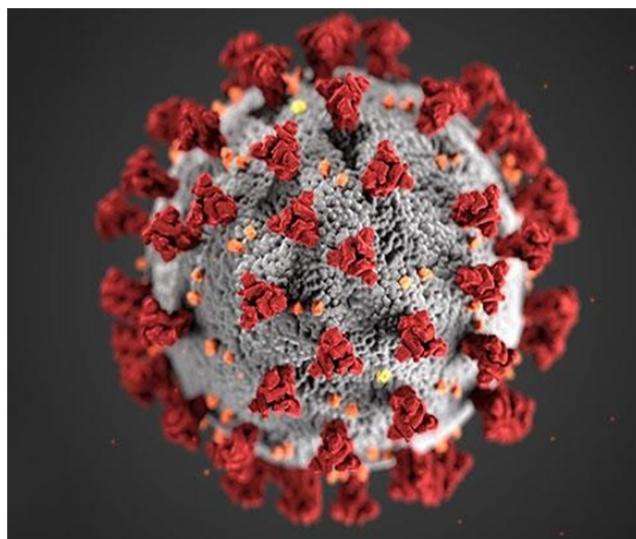
Table 1 Showing list of pandemics that affected human race in the past 100 years

Pandemic	origin	year	Death
Spanish Flu(H1N1)	Kansas U.S.A	1918-1920	17-100 million
Asian flu (H2N2)	China	1956-1958	2 million
1968 Flu Pandemic(H3N2)	China	1968	1 Million
2009 Flu Pandemic(H1N1)	U.S.A	2009	½ MILLION
HIV/AIDS	U.S.A	1980	25 MILLION
SARS COV	China's Guangdong province	2002	812
MERS	Saudi Arabia	2012	866
SARS COV 2(COVID 19)	China	2019	5 million

spread was the COVID appropriate behavior that the disease taught. Awareness was created across the country over a very large scale like never before about the proper use of masks , cough etiquettes , physical distancing hand washing and sanitization .People learnt the importance of a healthy diet and started practicing yoga and pranayama more diligently .They learned the value of simple ways to manage and monitor mild symptoms at home .With lock down and most of the people working from home not only did the spread of infection was controlled but also came an additional boon of increased cohesiveness amongst family members. People got time to nurture their talents and give time to their hobbies and hidden talents which were masked in the daily hustle and struggle of life. Many groups of people came forward to help patients and families suffering due to COVID 19. The lockdown and proper use of masks during the COVID-19 pandemic not only helped in controlling the viral infection but to a great extent helped in reducing the burden of air borne diseases including Tuberculosis ² in India. Therefore, its origin, spread and control were a learning not only for the medical fraternity but the entire Indian population as a whole.

COVID 19 VIRUS

The coronavirus disease 2019 (Covid-19) is a global pandemic that was first detected in China in December, 2019. It is called corona because in Latin corona means crown and this virus has crown shaped appearance due to the presence of spike proteins in its structure It is a viral infection with an incubation period of 2 to 14 days. About 25% to 50% patients with COVID-19 may remain



Asymptomatic, however they may be carrier and may spread the disease to others with whom they come in contact.

Symptomatic patients present with Mild symptoms in 81% of the cases, Moderate to severe symptoms in 14% and Critical illness in 5% of the cases ³.

The virus spreads from infected person via usually inhaling droplets released from coughing and sneezing, from infected aerosols since the virus remain viable in air for 3 hours and from contaminated objects (Fomites/Inanimate objects). So, a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes.

Table 2 Showing the viability of Corona Virus on various objects

SURFACE	VIABILITY PERIOD
Aerosols	3 hours
Copper	4 hours
Cardboard	24 hours
Stainless steel	48 hours
Plastics	72 hours
Shoes	5 days

Ref-Aerosol and Surface Stability of SARS-CoV-2asCompared with SARS-CoV-1. New England Journal of Medicine.;2:2020.

The infection of the virus causes a multisystem inflammatory response in the body that can lead to both pulmonary and extrapulmonary complications. Pulmonary complications include acute respiratory distress syndrome, pneumonia, pneumothorax, pulmonary fibrosis, etc. Amongst the extrapulmonary complications the most frequently encountered are Septic Shock, Acute Kidney Injury, Disseminated Intravascular Coagulation, Rhabdomyolysis Acute Cardiac Injury leading to Fulminant Myocarditis and Arrhythmia ⁴.

The second wave of this deadly disease emerged with new mutant variant with higher virulence and

higher mortality. It was also quite different from its first wave. In the second wave of COVID patients showed multisystem involvement and the symptoms

were not just confined to the lungs, middle aged and even young population was also equally affected⁵.

Table 3 showing differences between First and second wave of Covid 19

	FIRST WAVE	SECOND WAVE
Causative organism	SARS-Cov-2 virus	Several mutants of SARS-Cov-2 virus
Knowledge about the disease	Less	More
Symptomatology	More related to respiratory system	Newer symptoms like Gastrointestinal etc. adding; any new symptom can be due to covid 19
Presentation	Less intense and self-limiting	More intense and prolonged
Positivity rate	Lower	Much higher
Shortness of breaths	Less cases with breathlessness	More cases with breathlessness
Age profile of the patients	Relatively less younger population	Relatively More younger population
Health care workers	<ul style="list-style-type: none"> •Lesser trained people •Fear of acquiring infection •Not vaccinated 	<ul style="list-style-type: none"> •More trained increased •Lesser fear to acquire infection •Mostly vaccinated
Bed capacity	Limited	Enhanced
Ventilator beds	Less than 25000	Increased to more than 50000
Laboratory testing	Only one laboratory in January 2020	More than 2000 laboratories
PPE	Scarcity	Plenty PPE produced; India is the second largest producer of PPE kits
N95 mask production	less	Large /plenty
Vaccine	Not available	Three vaccines available and three more approved (Moderna, Pfizer and Zycov-D)
Treatment affordability	<ul style="list-style-type: none"> •Increased test price •Increased treatment cost and PPE 	<ul style="list-style-type: none"> •Markedly reduced test price •Reduced treatment cost and PPE
Oxygen requirement to the patient	Less	More
Requirement of mechanical ventilation	Less	More
Disease Spread	Slower	Much faster
Plasma Therapy	Limited	Of no use ;removed from ICMR Protocol
Remdesivir and tocilizumab	Main treatment	Now off labelled
Ivermectin	Noticed increasing use of ivermectin in treatment and prophylaxis but not included in ICMR protocol	Noticed the rampant use of ivermectin and included in ICMR Protocol
Complication	less	More, like black fungus, pneumothorax, pneumomediastinum, heart attack, stroke ,respiratory failure

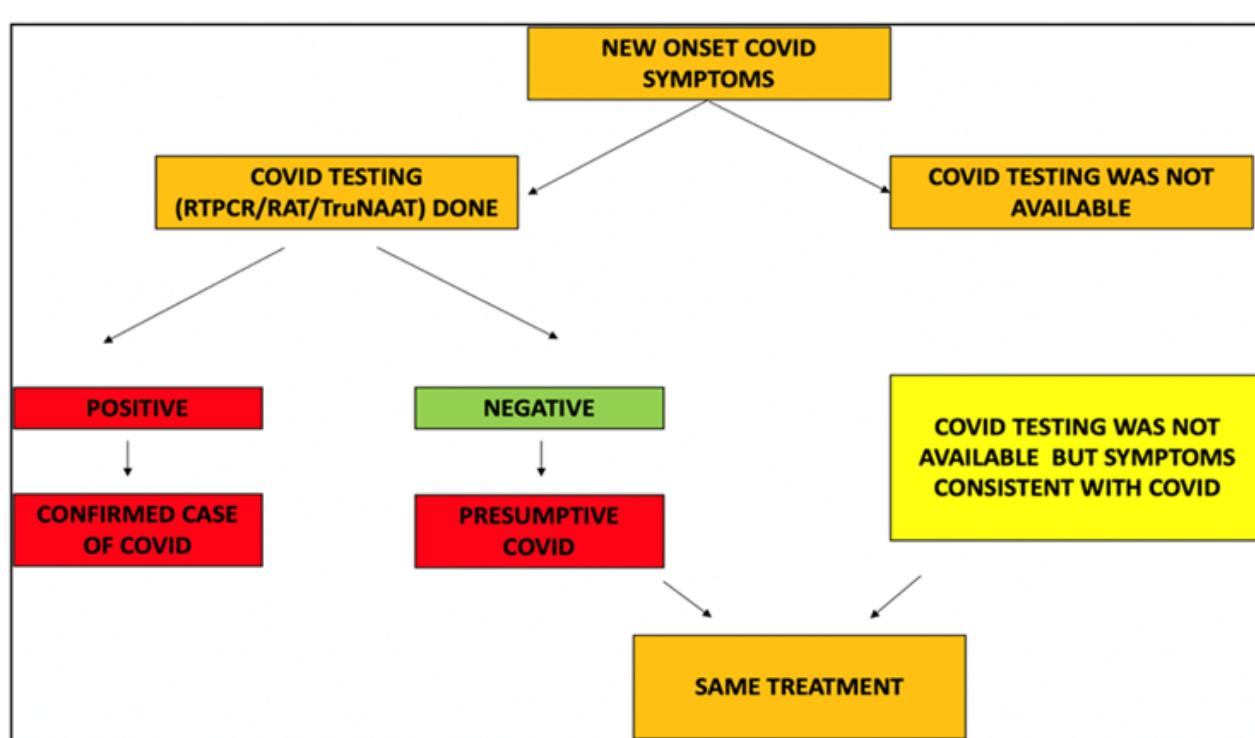
Ref Jain VK, Iyengar KP, Vaishya R. Differences between First wave and Second wave of COVID-19 in India. Diabetes & Metabolic Syndrome. 2021 May 8.(Modified)

The 2nd wave in India nearly collapsed the health care system and the entire country was panic struck and helpless⁶. The patients that were admitted were having a very prolonged hospital stay and so patient turnover was very poor and therefore, less availability of hospital beds became a major concern. The crisis of life saving gas oxygen made the situation even worse. Indian government understood the seriousness of the situation and acted promptly in resolving it as a result various new oxygen delivery plants were set up within no time, industrial oxygen was diverted for medical use, Prime Minister launched 'OXYGEN EXPRESS' train for rapid transport of oxygen from producer to people. Indian doctors played a very big role in this pandemic. They rendered their services 24 X7 and selflessly owing to which the Indian mortality was far less than global mortality. Nearly 798 Indian doctors Sacrificed their lives during the 2nd wave of COVID-19 while serving the sick⁷. Not only COVID-19 virus produced immediate symptoms but also long term affects, popularly known as "LONG COVID".

My Personalized Perspective

Fighting COVID pandemic in India was a big challenge because of the population size and poor healthcare infrastructure. Furthermore, there was a vast diversity in the availability of healthcare facilities between rural and urban India and around 70 % of the Indian population resides in villages.

The scarcity of medical resources in rural India was unmasked during the COVID pandemic. The doctor-patient ratio of 1:6300 was way too less⁸ than the ratio suggested by the World Health Organization (WHO) in this regard (1:1000). This ratio was even lesser in villages and tribal areas. The relocation of the urban crowd to small towns and villages post-lockdown led to a surge in rate of Covid infection in rural India. Other than the low doctor patient ratio there were various other challenges that the country faced in managing COVID specially in its villages like lack of basic transportation, less number of available ambulance services, lack of standards of home isolation because of small overcrowded



Simplified algorithm designed by Dr Surya Kant for the approach to COVID treatment in rural areas where facility of COVID testing is not available

Figure 2-Simplified algorithm designed by Dr Surya Kant for the approach to COVID treatment in rural areas and remote areas

houses. Even the facility of COVID testing were not available everywhere and not all had access to medicines for combating COVID infection. These problems were a hurdle in providing optimum health care facilities to all fellow residents of the country even though government tried its best to make facilities accessible to the entire population of the country. To cater this problem, I also came up with a pulse oximeter-based treatment strategy to initiate the basic treatment of Covid-19⁹.

Me along with a group of senior doctors with vast clinical experience looked at Ivermectin, one of the old molecule and evaluated it's use in COVID 19 management. After critical panel discussion, we all came to a conclusion that Ivermectin can be a

potential molecule for prophylaxis and treatment of people infected with Coronavirus, owing to its anti-viral properties coupled with effective cost, availability and good tolerability and safety. Following this White paper on Ivermectin as a potential therapy for COVID 19 came in July 2020 which later also became a part of global literature on coronavirus diseases available on the official World Health Organization webpage¹⁰. The Government of UTTAR PRADESH within no time organized a meeting of experts and released a government order stating the use of ivermectin in the treatment of COVID19.

Ivermectin became a wonder drug in management and prevention of COVID infection specially in resource poor locations of the country ^{11,12}. When

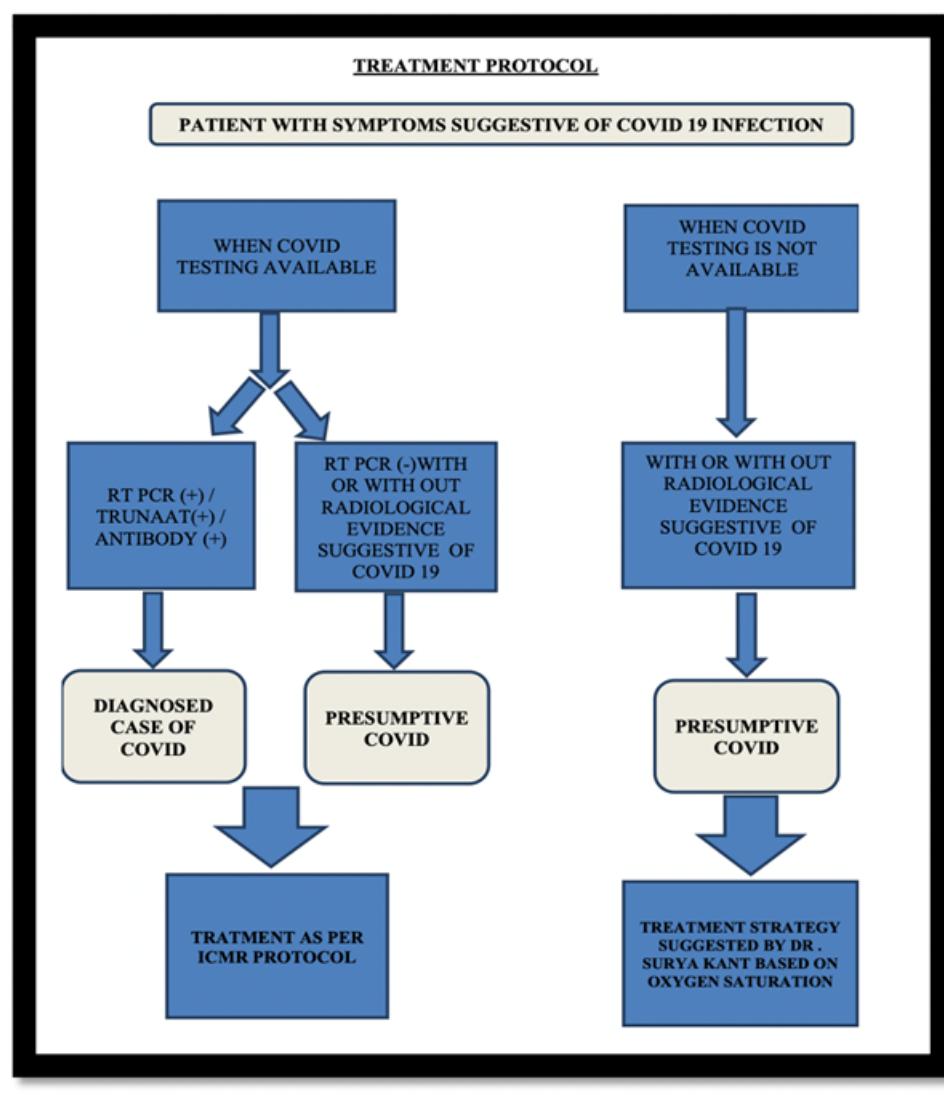


Figure 3- SIMPLIFIED covid treatment protocol by Dr Surya Kant

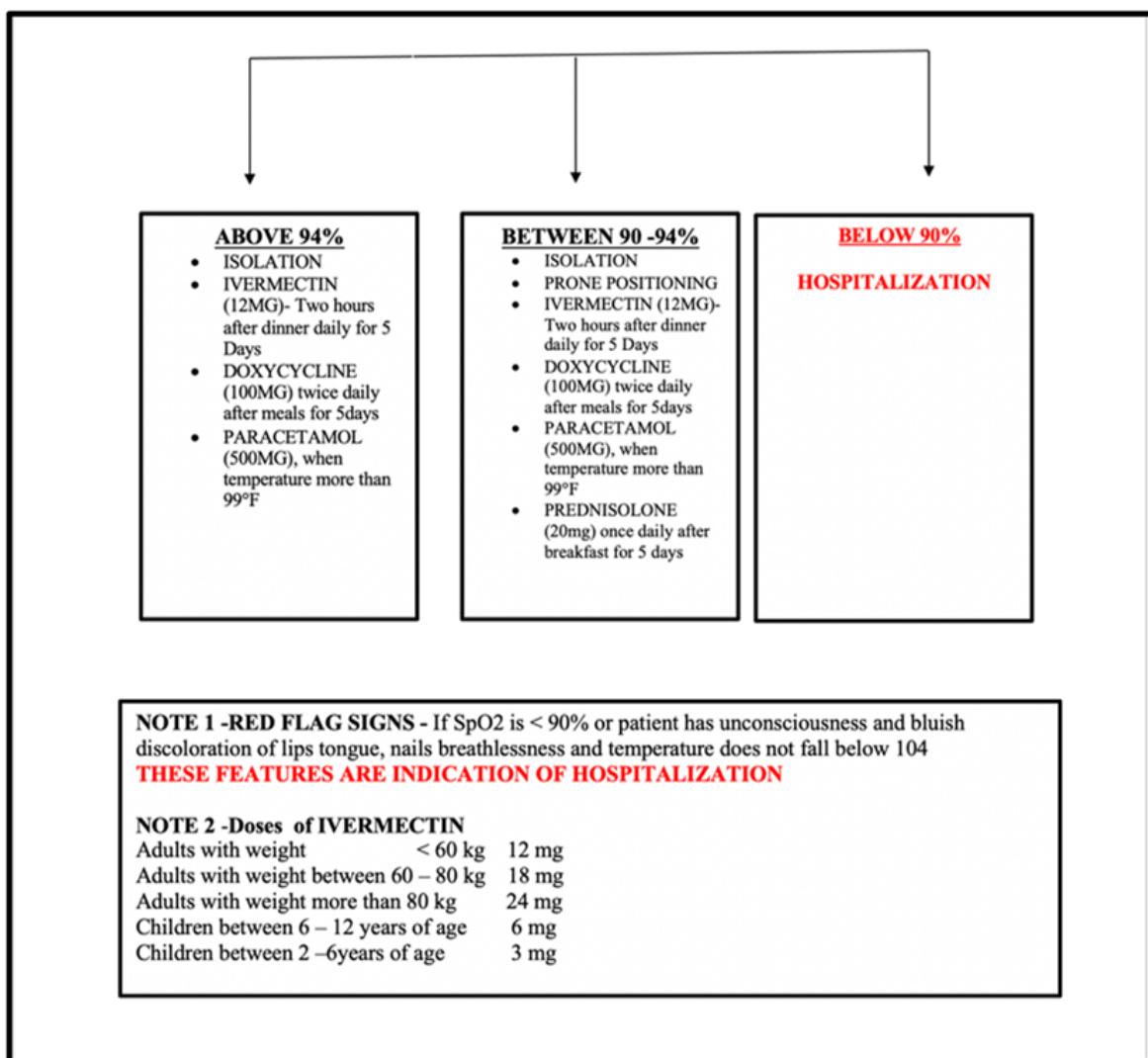


Figure 4 -Modified Treatment Protocol of Dr Surya Kant for COVID 19 based on pulse oximeter reading only

antiviral drugs like hydroxychloroquine¹³, remdesivir¹⁴and favipiravir¹⁵ were questioned regarding their efficacy ivermectin continued to show its effect in managing and preventing COVID infection. Rationale and timely use of steroids by Indian doctors also led to a decreased mortality rate and prevention of disease progression. All doctors over the country including me were involved in crushing the pandemic and decreasing the intensity of the massacre caused by the pandemic. I myself was continuously involved in all ways and forms , from administration to action in order to curb its spread and spread awareness about the disease .I was The State trainer for COVID and was involved in covid related training in various medical colleges of the state , I was In charge of virtual rounds of all COVID hospitals in the district as well as In charge of all

COVID related affairs in King George's Medical University ,UP , Lucknow during the second wave of COVID when it was a 1100 bedded COVID hospital ,along with this I believe that more often the threat of the disease in the major culprit rather the disease itself .Therefore , I was continuously and religiously also involved in spreading awareness on various virtual platforms through talks and webinars so that I could cater to the common queries and myths of the people and at the same time spread basic necessary information pertaining to the disease.With all the hurdles faced by the country during both the waves of COVID 19 with the support of the government and the with the tremendous contributions and sacrifices of the medical fraternity India was able to cater and combat the major crisis of the pandemic.

Vaccination

Vaccines against COVID-19 have been developed in record time thanks to important technological advances and labs all across the globe including India that have worked so hard for developing the golden bullet against COVID 19. Time taken by them for the development of vaccines was less, this does not imply that the process was not rigorous and that the usual steps were not followed. Clinical trials were expedited and not only did India participate in procuring the vaccines for its entire population but also made its own indigenous vaccine. Various vaccine targets were studied [Figure 5] and researched to come up with the final vaccine which was effective in preventing the disease.

Covaxin was India's first indigenous, whole-virion, inactivated vaccine developed by Bharat Biotech in collaboration with the Indian Medical Research Council (ICMR) and the National Institute of Virology (NIV). In July 2021, Bharat Biotech reported the vaccine to be 78% effective against symptomatic cases, 93% effective against severe COVID-19 infection and 65% effective against the Delta variant. Bharat Biotech's Covaxin Covid-19 vaccine trials for children aged 2-18 years are currently underway and its results are likely to be out very soon.

Covishield on the other hand is the Indian modification of the Oxford–AstraZeneca COVID-19 vaccine in which instead of chimpanzee Adeno virus Human Adeno virus is used. ZyCoV-D is another

indigenous plasmid DNA vaccine by Ahmedabad-based pharmaceutical major Zydus Cadila, which when injected produces the spike protein of the SARS-CoV-2 virus and elicits an immune response mediated by the cellular and humoral arms. It was also the first COVID-19 vaccine that has been tested in adolescent population in the 12-18 years age group in India. Currently 3 vaccines are in use, however emergency use authorization has been given for 3 more vaccines –

1. Moderna
2. Johnson &Johnson
3. Zydus Cadila Zycova -D (3 Doses, For 12 years and above) (Table 4)

COVID-19 vaccines present the most plausible intervention to sustainably control the pandemic. The scale and challenges of the COVID-19 vaccination campaign are unprecedented. A coordinated, evidence- based education, communication, and behavioural intervention strategy is essential ¹⁶.

Indian vaccination drive began on 16th January 2021 with its first phase in which 66 lakh healthcare workers got their 1st dose and 24lakh were vaccinated with both the doses. I was the first doctor to receive COVID vaccine shot in King George's Medical University , UP , Lucknow on the very first day when COVID vaccination drive of India began (16/1/2021) following which I also became The

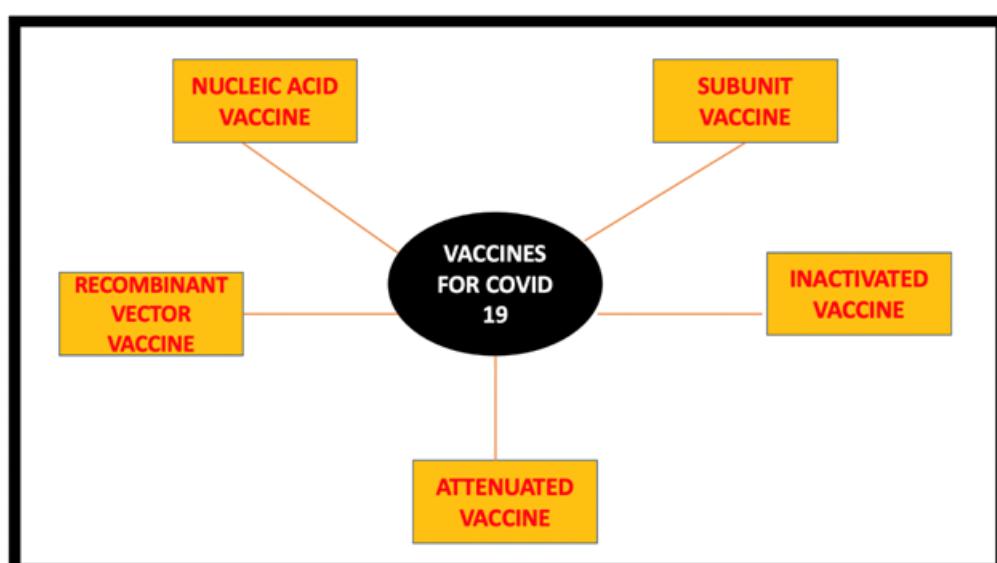


Figure 5 -Types of COVID vaccines available

Table 4- COVID vaccines available in India

Name/Company	Type	Efficacy	Doses	Interval between doses
Covaxin (Bharat Biotech)	Inactivated Virus Vaccine	77.8%	2	4 Weeks
Covishield (Oxford-AstraZeneca)	Viral Vector	70.42%	2	12 Weeks
SPUTNIK V	VIRAL VECTOR	91.6%	2	3 Weeks

Brand ambassador for COVID vaccination under the National Health mission .Within 45 days on march 1st 2021 the country began its 2nd phase of vaccination by Opening up vaccination for over 60 years of age and those above 50 years with co-morbidities .Just after one month the government began the third phase of vaccination in which the drive was opened for age group 45 and above irrespective of co-morbidities from April 1,2021.Finally on May 1st 2021 vaccination was open for all above the age group of 18 years of age . With the rapid spread of awareness about vaccination amongst the population India made a world record by vaccinating 2.5 crore people as on 17th September 2021 on the occasion of the Prime Minister's birthday which was followed by the historical landmark on October 21st when the cumulative doses of administered COVID 19 vaccines surpassed 100 crores and it was commendable that this milestone was achieved just within 9 months of the starting of this huge vaccination drive. The vaccination drive has been boosted with the availability of surplus of vaccines and the initial hesitancy of getting vaccinated has also decreased and more and more people are coming up and getting themselves vaccinated now.

Conclusion

India as always as a country has stood steadily against the unprecedented challenge caused by the spread of COVID-19 infections, with both government and non-governmental cooperation augmenting diagnostic , health care and research facilities along with the mass propagation of

awareness regarding the basic ways to safeguard oneself from COVID or any other infective disease .The emergence of COVID 19 in our country has also been a boon with respect to so many things that it has taught that we were less aware of .The most important amongst it is the Covid Appropriate behavior because no matter what be the variants that emerge, no matter what be the new mutants that we see, if we are able to maintain physical distance, wear mask properly, wash our hands, and prevent crowd from gathering then we will not allow the virus to spread , rather this will curtail the spread of any infectious disease including tuberculosis .The Public has now become wiser and aware on how to be healthy and have a check on their vitals via Pulse Oximeter for Oxygen saturation, Prone Position to maintain the oxygen levels, Eating healthy Diet to improve their Immunity. People now understand the importance of social distancing and other preventive measures prescribed by the government with good attitude. The credit of the victory against the COVID pandemic undoubtedly goes to the unyielding efforts of the doctors who even sacrificed their lives while treating and providing their services in the pandemic. Nearly 1500 doctors lost their lives in the pandemic and in order to pay homage to their skills all of them should be given the title COVID martyrs or CORONA SHAHEED and their efforts and sacrifices should be remembered forever. COVID was a monster and a tutor at the same time so, If, we keep following the things this pandemic has taught us we can not only easily seize the surge of the third wave but also be protected against the spread of any upcoming future pandemic

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INTRODUCTION

Several cases of acute atypical pneumonia were reported from Wuhan, China in December 2019. The pathogen responsible for the atypical pneumonia was found to be a novel coronavirus named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was seen to be highly homologous to the SARS coronavirus (SARS-CoV), which was responsible for the SARS during the 2002–2003. The respiratory illness caused by this virus was termed as coronavirus disease 2019 (COVID-19) by the WHO. The outbreak was considered to have started via a zoonotic spread from the seafood markets in Wuhan, China. Subsequently, rapid human-to-human transmission has spread globally and was declared a pandemic by the WHO on March 11, 2020.

VIRAL LIFE CYCLE AND HOST CELL INVASION

The virus is transmitted via respiratory droplets and aerosols from person to person. SARS-CoV 2 is highly virulent and the transmission capacity is greater than the previous SARS virus (outbreak in 2003), with high abundance in infected people (up to a billion RNA copies/mL of sputum) and long-term stability on contaminated surfaces. Once inside the body, the virus binds to host receptors and enters host cells through endocytosis or membrane fusion. The coronaviruses are made up of four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. The S protein is seen to be protruding from the viral surface and is the most important one for host attachment and penetration. Once inside the body, the virus binds to host receptors and enters host cells through endocytosis or membrane fusion. The coronaviruses are made up of four structural proteins, namely, the spike (S), membrane (M),

envelop (E) and nucleocapsid (N) proteins. The S protein is composed of two functional subunits (S1 and S2), among which S1 is responsible for binding to the host cell receptor and S2 subunit plays a role in the fusion of viral and host cellular membranes.

ACE-2 has been identified as a functional receptor for SARS-CoV and is highly expressed on the pulmonary epithelial cells.⁽¹⁾ It is through this host receptor that the S protein binds initially to start the host cell invasion by the virus by viral and host cell membrane fusion.

Postmembrane fusion, the virus enters the pulmonary alveolar epithelial cells and the viral contents are released inside. The viral N protein binds the new genomic RNA and the M protein facilitates integration to the cellular endoplasmic reticulum. These newly formed Nucleocapsids are then enclosed in the ER membrane and transported to the lumen, from where they are transported via golgi vesicles to the cell membrane and then via exocytosis to the extracellular space. The new viral particles are now ready to invade the adjacent epithelial cells as well as for providing fresh infective material for community transmission via respiratory droplets.

PATHOPHYSIOLOGY OF COVID-19

The type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE 2 and activating the SARS-CoV-2 S protein, which mediates the virus entry into host cells.⁽²⁾ ACE2 and TMPRSS2 are expressed in host target cells, particularly alveolar epithelial type-II cells. Similar to other respiratory viral diseases, such as influenza, profound lymphopenia may occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response, consisting of both the

innate and the adaptive immune response, impairs lymphopoiesis and increases lymphocyte apoptosis.

In later stages of infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised. In addition to epithelial cells, SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils. Autopsy studies have shown diffuse thickening of the alveolar wall with mononuclear cells and macrophages infiltrating airspaces in addition to endothelialitis.⁽³⁾ Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground-glass opacities on computed tomographic imaging. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS). Bradykinin-dependent lung angioedema may also contribute.

The development of viral sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, may further contribute to multiorgan failure.⁽⁴⁾

PATHOGENESIS OF THROMBOSIS IN COVID-19

In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur. A report from Wuhan, China, indicated that 71% of 183 individuals who died of COVID-19 met criteria for diffuse intravascular coagulation.⁽⁵⁾ The ACE2 receptor is also widely expressed in the cardiovascular system. Therefore, there are multiple cardiovascular implications of COVID-19 as well. The pathophysiology of thromboembolism in COVID-19 compared with non-COVID-19 disorders may be more platelet-dependent and related to viral mediated endothelial inflammation, in addition to hyper-coagulability associated with increased concentrations of coagulation factors, acquired antiphospholipid antibodies, and decreased concentrations of endogenous anticoagulant proteins.⁽⁶⁾ Because of the tropism of SARS-CoV-2 to type II pneumocytes, the virus can interface with a large area of the pulmonary microvasculature. SARS-CoV-2 also has tropism for glomerular capillary loops, small intestine capillaries, and myocardiocytes.⁽⁷⁾

SARS-CoV-2 can infect the pericytes and perivascular cells present on the abluminal surface of microvessels, where they are embedded in the basement membrane. Cell infection and induced inflammation in pericytes and endothelial cells may promote local apoptosis and potent inflammatory cytokines. Because of the potent local and systemic cytokine production, the platelets are activated and interact with neutrophils. The neutrophil extracellular trap (NET)osis process may also stimulate thrombin production and fibrin deposition. The excess of fibrin deposition and fibrinolysis shutdown lead to intravascular thrombosis and, finally, to clinical thromboembolic complications.

Wide-spread vascular abnormalities in autopsy specimens from patients with Covid-19 pneumonia, including thrombosis, microangiopathy, and a higher degree of angiogenesis than was seen in patients with influenza pneumonia.⁽⁸⁾ Focal vessel enlargement within ground-glass opacities was described in early imaging investigations of Covid-19. Additional extensive vascular abnormalities, including regionally dilated segmental and subsegmental pulmonary vessels, increased branching and tortuosity of pulmonary vasculature, and perfusion abnormalities were also noted on dual-energy CT.⁽⁹⁾ Interestingly, PE can be found without associated DVT.⁽⁹⁾ Hence, Thromboprophylaxis should be considered for all hospitalized patients with COVID-19 in the absence of contraindications.⁽⁶⁾

The predominant coagulation abnormalities in patients with COVID-19 suggest a hypercoagulable state, which has been termed thrombo-inflammation or COVID-19-associated hemostatic abnormalities (CAHA). The most consistent observation among patients with COVID-19, particularly those with severe illness, is D dimer elevation.

In normal lung physiology, the pulmonary alveolar space has been considered as a profibrinolytic environment. However, in patients with ARDS, the fibrinolytic system is often suppressed because of increased plasminogen activator inhibitor I in both plasma and the bronchoalveolar lavage fluid. Moreover, plasmin also cleaves numerous matrix proteins but, more important, also misfolded/

necrotic proteins, which can be of significant importance in patients with COVID 19. In CAHA, elevated D dimer levels are a common feature, and this suggests that the endogenous fibrinolytic system is functional.

Patients with COVID 19 who develop a hyperinflammatory state may advance to severe manifestations with cytokine storm and multiple organ failure. The cytokine storm, which includes interleukin 1, interleukin 6, and tumour necrosis factor, can either affect pre-existing atherosclerotic lesions or promote accelerated atherogenesis and also promote lesion thrombogenicity. Moreover, systemic cytokines can stimulate adhesion molecule expression and increase the recruitment of inflammatory cells. These alterations may enhance the vulnerability of pre-existing plaques to rupture or promote accelerated atherogenesis.

On the other hand, the hyperinflammatory response may also be related to a nonobstructive disease, such as stress cardiomyopathy (Takotsubo), because of the intense release of potent inflammatory cytokine and sympathetic surge.

PATHOGENESIS OF MIS-A and MIS-C IN COVID-19

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition in children and adolescents infected with SARS-CoV-2, the virus that causes COVID-19. Since June 2020, there have been several reports of a similar multisystem inflammatory syndrome in adults (MIS-A).

PHASE I: Early infection with SARS-CoV-2 is likely to be asymptomatic or mildly symptomatic in children.

PHASE II: The pulmonary phase is severe in adults but is mild or absent in many children.

PHASE III: The early infection appears to trigger macrophage activation followed by the stimulation of T-helper cells. This in turn leads to cytokine release, the stimulation of macrophages, neutrophils, and monocytes, along with B-cell and plasma cell activation with the production of antibodies leading to a hyperimmune response.

This immune dysregulation is associated with the inflammatory syndrome in affected children. Direct infection with SARS-CoV-2 is less likely to play a role in MIS-C. The majority of published cases have had positive serologic testing for SARS-CoV-2 (60/69, 87%) and less commonly positive RT-PCR testing from nasopharyngeal testing (23/70, 32%), suggesting that this syndrome may be post-infectious rather than related to acute early infection.

In adults with severe respiratory failure from SARS-CoV-2 infection, who typically experience clinical deterioration about 1 week following illness onset, a dysregulated immune system is thought to drive disease manifestations, as opposed to direct cellular injury from viral infection. Children appear to have less severe pulmonary manifestations compared to adults, possibly due to lower gene expression of the angiotensin converting enzyme (ACE)-2 receptor.

Immune dysregulation in adults with respiratory disease is characterized by lymphopenia (specifically NK cells, CD4 T lymphocytes and B lymphocytes) and sustained production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF)- α and interleukin (IL)-6. This immune dysregulation has been the basis of immunomodulatory therapies for adults with severe SARS-CoV-2 infection, such as tocilizumab, a humanized monoclonal antibody against the IL-6 receptor. It is speculated that MIS-C is a delayed immunological phenomenon associated with inflammation (Stage III—hyperinflammation phase) following either symptomatic or asymptomatic COVID-19 infection.⁽¹⁰⁾

This entity has to be carefully distinguished from other known syndromes like kawasaki disease, toxic shock syndrome, secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome.

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Introduction:

In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan. The pathogen has been identified as a novel enveloped RNA betacoronavirus that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.

Clinical Features:

Conventional routes of transmission of SARSCoV, MERS-CoV, and highly pathogenic influenza consist of respiratory droplets and direct contact, mechanisms that probably occur with SARS-CoV-2 as well.

The incubation period for COVID-19 is generally within 14 days following exposure, with most cases occurring approximately four to five days after exposure.

Asymptomatic infections have been well documented. One review estimated that 33 percent of people with SARS-CoV-2 infection never develop symptoms.^[1]

Symptomatology of COVID 19:^[2]

The range of associated symptoms was illustrated in a CDC report as:

- Cough in 50 percent
- Fever (subjective or >100.4°F/38°C) in 43 percent
- Myalgia in 36 percent
- Headache in 34 percent
- Dyspnea in 29 percent
- Sore throat in 20 percent
- Diarrhea in 19 percent

- Nausea/vomiting in 12 percent
- Loss of smell or taste, abdominal pain, and rhinorrhea in fewer than 10 percent each.

Clinical manifestations differ with age. In general, older men (>60 years old) with co-morbidities are more likely to develop severe respiratory disease that requires hospitalization, or even die, whereas most young people and children have only mild diseases or are asymptomatic.

Spectrum of severity:^[3]

- Mild disease (no or mild pneumonia) was reported in 81 percent.
- Severe disease (eg, with dyspnea, hypoxia, or >50 percent lung involvement on imaging within 24 to 48 hours) was reported in 14 percent.
- Critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) was reported in 5 percent.
- The overall case fatality rate was 2.3 percent; no deaths were reported among noncritical cases.

Risk factors for severe illness —

Increasing age — Individuals of any age can acquire SARS-CoV-2 infection, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease. Older age is also associated with increased mortality.

Symptomatic infection in children and adolescents appears to be relatively uncommon; when it occurs, it is usually mild, although a small proportion (eg, <2 percent) experience severe and even fatal disease. Details of COVID-19 in children are discussed elsewhere.

Comorbidities —The United States CDC has created a list of certain comorbidities that have been associated with severe disease (defined as infection resulting in hospitalization, admission to the ICU, intubation or mechanical ventilation, or death) and notes that the strength of evidence informing the associations varies.^[4,5]

Established, probable, and possible risk factors (comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review [starred conditions], in observational studies, or in case series)

- Cancer
- Cerebrovascular disease
- Children with certain underlying conditions
- Chronic kidney disease
- COPD* and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis)
- Diabetes mellitus, type 1* and type 2*
- Down syndrome
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)*
- HIV
- Neurologic conditions, including dementia
- Obesity* (BMI >30 kg/m²) and overweight (BMI 25 to 29 kg/m²)
- Pregnancy*
- Smoking* (current and former)
- Sickle cell disease or thalassemia
- Solid organ or blood stem cell transplantation
- Substance use disorders
- Use of corticosteroids or other immunosuppressive medications

Possible risk factors but evidence is mixed (comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions)

- Asthma
- Hypertension
- Immune deficiencies

- Liver disease

Socioeconomic background and sex — Certain demographic features have also been associated with more severe illness.

Males have comprised a disproportionately high number of critical cases and deaths in multiple cohorts worldwide.

Black, Hispanic, and South Asian individuals comprise a disproportionately high number of infections and deaths due to COVID-19 in the United States and United Kingdom, likely related to underlying disparities in the social determinants of health [57,73-77].

Laboratory abnormalities — Particular laboratory features have also been associated with worse outcomes. These include [60,80-83]:

- Lymphopenia
- Thrombocytopenia
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin) and inflammatory cytokines (ie, interleukin 6 [IL-6] and tumor necrosis factor [TNF]-alpha)
- Elevated D-dimer (>1 mcg/mL)
- Elevated prothrombin time (PT)
- Elevated troponin
- Elevated creatine phosphokinase (CPK)
- Acute kidney injury

Viral factors — Patients with severe disease have also been reported to have higher viral RNA levels in respiratory specimens than those with milder disease, although some studies have found no association between respiratory viral RNA levels and disease severity.

Complications:

Respiratory failure – Acute respiratory distress syndrome (ARDS) is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnea.

Cardiac and cardiovascular complications – Arrhythmias, myocardial injury, heart failure, and shock.

Thromboembolic complications – Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in severely ill patients with COVID-19, particularly among patients in the intensive care unit (ICU), among whom reported rates have ranged from 10 to 40%.

Arterial thrombotic events, including acute stroke (even in patients younger than 50 years of age without risk factors) and limb ischemia, have also been reported.

Neurologic complications – Encephalopathy is a common complication of COVID-19, particularly among critically ill patients.

Stroke, movement disorders, motor and sensory deficits, ataxia, and seizures occur less frequently.

Inflammatory complications –

Cytokine Storm:

The “cytokine storm” results from a sudden acute increase in circulating levels of different pro-inflammatory cytokines including IL-6, IL-1, TNF- α , and interferon. This increase in cytokines results in influx of various immune cells such as macrophages, neutrophils, and T cells from the circulation into the site of infection with destructive effects on human tissue resulting from destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure, and ultimately death.

Guillain-Barré syndrome may occur, with onset 5 to 10 days after initial symptoms.

A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has also been described in children with COVID-19.

Symptoms of COVID-19 :

Common Symptoms:	Psychologic and neurocognitive	Uncommon Symptoms:
Fatigue Dyspnea Chest discomfort Cough Anosmia	Post-traumatic stress disorder Impaired memory Poor concentration Anxiety/depression Reduction in quality of life	Joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness, vertigo, myalgias, insomnia, alopecia, sweating, and diarrhea

In the rare adults in whom it has been reported, this syndrome has been characterized by markedly elevated inflammatory markers and multiorgan dysfunction (in particular cardiac dysfunction), but minimal pulmonary involvement.

Secondary infections – Cases of mucormycosis in patients with acute and recent COVID-19 have been reported in India; the incidence is uncertain, but some reports suggest that nearly 15,000 cases had occurred by the end of May 2021.

In a retrospective study from 16 health care centers in India, there were 187 cases of Mucormycosis among approximately 12,000 patients hospitalized with COVID-19 between September and December 2020 (prevalence 0.27 percent overall and 1.6 percent among ICU patients); most cases involved the rhino-orbital region. In this study and published case reports, diabetes mellitus and glucocorticoid receipt have been common risk factors.

Recovery and long-term sequelae:

The time to recovery from COVID-19 is highly variable and depends on age and pre-existing comorbidities in addition to illness severity.

Individuals with mild infection are expected to recover relatively quickly (eg, within two weeks) whereas many individuals with severe disease have a longer time to recovery (eg, two to three months).

The most common persistent symptoms include fatigue, dyspnea, chest pain, cough, and cognitive deficits.

Data also suggest the potential for ongoing respiratory impairment and cardiac sequelae.

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1. Introduction

The CoronaVirus Disease 2019 (**COVID-19**) pandemic, caused by the **Severe Acute Respiratory Disease Corona Virus 2** (SARS-CoV-2), has led to millions of confirmed cases and deaths worldwide. Since the beginning of the pandemic till date, there have been more than 232 million confirmed cases with more than 4.7million deaths. Early and definitive diagnosis plays a pivotal role in patient management as well as in reducing transmission of the disease in order to control the pandemic. The present article aims to give an overview of the commonly used and Novel laboratory methods for the diagnosis of COVID-19, with a brief discussion on the principles, interpretation, advantages and limitations of the commonly used methods. Readers are advised to refer to national and international guidelines for detailed discussion of all aspects of diagnosis, management and control of COVID-19.

2. SARS-COV-2 structure and genome:

Knowledge regarding the structure and genomic organization of SARS-CoV-2 is essential for understanding the methods for the laboratory diagnosis of COVID-19 [Fig.1&2]. SARS-CoV-2 was first isolated and sequenced in China in January 2020. It is a enveloped ,positive strand RNA virus belonging to the *Coronaviridae* family, genus *Beta corona virus* and sub genus *Sarbeco virus* and on the genetic level shares 96%, 80%, and 50% sequence identities with the bat coronavirus (RaTG13), SARSCoV-1, and Middle East respiratory syndrome coronavirus (MERS-CoV) respectively.

3. Clinical spectrum

The clinical spectrum of COVID 19 may vary from asymptomatic infection to severe disease with life threatening complications. In most symptomatic cases, COVID-19 presents as a mild to moderate

upper respiratory illness, with signs and symptoms compatible with those of other respiratory viruses. Because of the nonspecific clinical presentation and atypical presentations being increasingly recognized, accurate diagnosis cannot be done clinically as neither the presence nor the absence of any sign or symptom can be used to rule in or out COVID-19. Biomarkers and Imaging are not sensitive or specific enough to definitively diagnose COVID-19. Laboratory methods for the detection of SARS-CoV-2 are thus essential for confirming the diagnosis of COVID 19 and several commonly used and novel methods have been developed since the start of the pandemic. (Fig 1: Structure of the SARS-CoV-2 Virus - Refer to color pages section)

4. Laboratory tests for diagnosis of COVID-19 :Commonly used and Novel tests under development

I) Molecular Methods for Viral RNA Detection

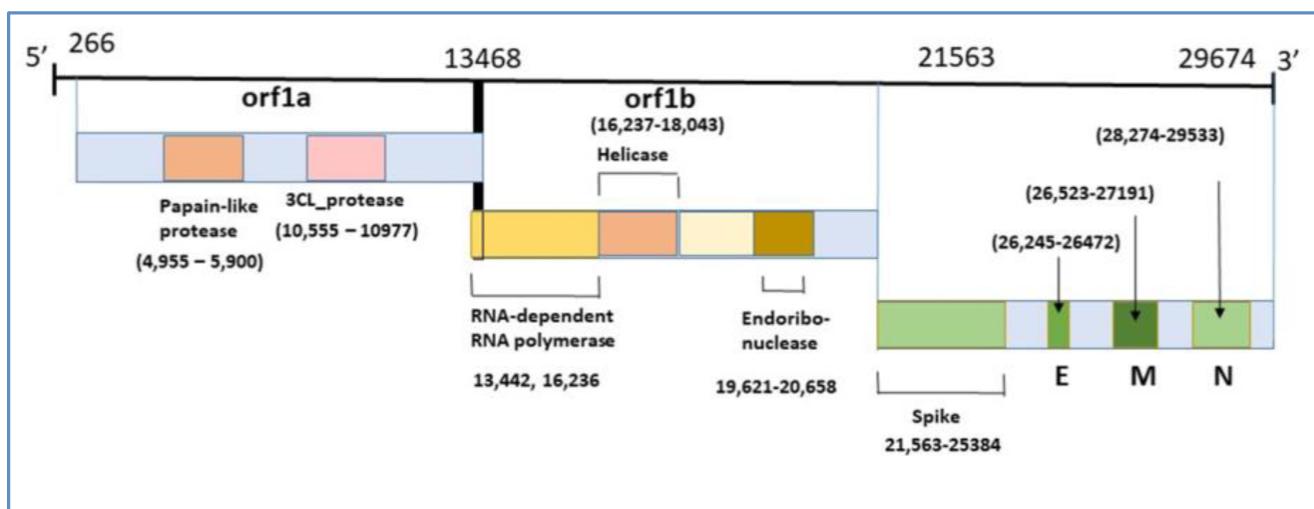
A) Real-time RT-PCR(Reverse transcription Polymerase chain reaction):

- Manual/semi-automated testss
- High throughput automated testss
- Rapid diagnostic tests (RDT)

B) Isothermal amplification technologies:

- Reverse transcription-recombinase polymerase amplifications
- Transcription-mediated amplification (TMA)s
- Nicking enzyme-assisted reactions
- Reverse transcription-loop-mediated isothermal amplifications
- CRISPR-Cas technology

C) SARS-CoV-2 next-generation sequencing



The regions that encode Open Reading Frames (ORFs) 1a and 1b, which encode the nonstructural polyproteins (nsp1-16, helicase, 3CL-pro and PL-pro, RNA- dependent RNA polymerase (RdRp), as well as the spike, envelope, membrane, and nucleocapsid structural proteins are indicated. Molecular assays for COVID- 19 diagnosis are designed to detect one or more of the above gene targets.

Fig. 2: The genomic organization of the 29,674-nucleotides of the SARS-CoV-2

II) SARS-COV-2 Antigen detection tests

- Lateral Flow Immunoassays(Rapid antigen tests)

III) Serological Immuno Assays for SARS-CoV-2 antibody Detection

- Enzyme-linked immunosorbent assay (ELISA)?
- Chemiluminescence immunoassay (CLIA)?
- Fluorescent microparticle immunoassays?
- Lateral flow immunoassays (Rapid Antibody Tests)
- Virus Neutralization assays

4.1. Performance characteristics of the tests:

- Some are Rapid (results available within minutes)/ others require time for processing.
- Some must be performed in a laboratory by trained personnel, some are point-of- care, and others can be performed at home or anywhere.
- Some tests are very sensitive (i.e., few false-negative results or few missed detections of SARS-CoV-2); others are very specific (i.e., few false-positive results or few tests incorrectly identifying SARS-CoV-2 when the virus is not

present); and some are both sensitive and specific.

- Some tests can be performed frequently because they are less expensive, easier to use, and supplies are readily available.

4.2. Selection and interpretation of SARS-CoV-2 tests: this should be based on-

- the context in which they are being used-

- **Diagnostic testing** is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with COVID- 19, or is asymptomatic but has recent known or suspected exposure to SARS- CoV-2.

- **Screening**-recommended for unvaccinated people to identify those who are asymptomatic and do not have known, suspected, or reported exposure to SARS-CoV-2. Screening helps to identify unknown cases so that measures can be taken to prevent further transmission.

- the prevalence of SARS-CoV-2 in the population being tested
- the performance characteristics of the tests

4.3. Important considerations for specimen collection for lab. diagnosis of COVID:

Accurate detection of any infectious disease requires adequate specimen collection at the anatomical site of infection, at a time when the pathogen of interest should be present.

- Specimen type:
- **Swabs** from the Upper respiratory tract are most commonly collected for tests which involve detection of SARS-CoV-2 RNA and Antigen.
- **Serum** is collected for serological tests which detect SARS-CoV-2 antibodies.
- For SARS-CoV-2 as for other respiratory viruses- specimens collected from the upper respiratory tract using a flocked (synthetic fibre) nasopharyngeal (**NP**) swab on thin plastic or wire shafts that are placed in universal or viral transport medium (**UTM or VTM**, respectively) are the gold standards;

This allows for enhanced recovery of the pathogen and stable transport to the laboratory with minimal sample deterioration and avoids the potential complications due to breakage of wooden sticks.

- Cotton swabs on wooden sticks -not recommended
- Alternatives to NP swab such nasal mid turbinate swabs, sampling of the anterior nares (Na), oropharyngeal (OP) swabs, or washes/aspirates from the nasopharynx, nose, or throat –require further validation.
- **Specimen combinations** can also be used; for e.g. NP swab along with OP swab or OP swab along with swab from the anterior nares. Both swabs should be placed in the same tube of VTM to increase sensitivity of detection.
- Global supply chain shortages led to development of **3D-printed swabs** and different transport media as alternatives to the recommended methods.
- **Additional specimen types** based on the clinical presentation –

- Specimens such as **BAL fluid, endotracheal secretions, or sputum** should be considered in hospitalized adults with progression of COVID-19 to **lower respiratory tract disease**.
- Non invasive specimens such as throat gargles, saliva are under evaluation.
- SARS-CoV-2 RNA has been detected from **stool** in the presence or absence of gastrointestinal symptoms-
- possibility of feco-oral transmission and human health or ecological risks.
- opportunity for research into community-based surveillance in low-prevalence settings using wastewater.
- Postmortem specimens-
- NP swabs, swabs from the lungs, and tissue samples can be used for diagnostic testing for SARS-CoV-2
- Samples should not be preserved in Formalin as RNA can be degraded by formalin and sensitivity for the detection of SARS-CoV-2 RNA by real-time RT-PCR could be compromised.

Timing of Specimen Collection[Fig.3]

CATCHING COVID-19

Different types of COVID-19 test can detect the presence of the SARS-CoV-2 virus or the body's response to infection. The probability of a positive result varies with each test before and after symptoms appear.

- **PCR-based tests** can detect small amounts of viral genetic material, so a test can be positive long after a person stops being infectious.
- **Rapid antigen tests** detect the presence of viral proteins and can return positive results when a person is most infectious.
- **Antibody tests** detect the body's immune response to the virus and are not effective at the earliest phase of infection.

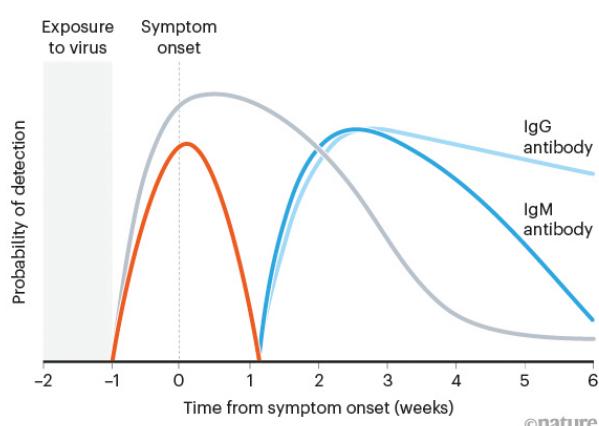


Fig 3.Timeline for COVID-19 diagnostic tests
(Source:Guglielmi,Nature,2020)

- o SARS-CoV-2 has been identified in various clinical specimen types, but the timing of detection differs between methods and the specimen types collected for testing.
- o The magnitude nitude of the viral load and duration of shedding depend on:
 - the specimen type,
 - the anatomical site of illness,
 - the severity of illness,
 - the host immune response to infection .
- o The timing of specimen collection is critical, as **testing too early or too late** following exposure can **potentially lead to false-negative results**.

For Real time RT-PCR

- o **false-negative rates could be minimized by testing 2 to 3 days after symptom onset**, with an average time of symptom onset of 5 days post exposure.
- o **Repeat testing** can be considered for individuals with an initial negative test result but for whom there is a high level of clinical suspicion.

For Antigen tests:

- o Antigen detection tests can detect SARS-CoV-2 antigen reliably when the viral load is high in the clinical specimens (i.e., typically from 1 to 3 days before the onset of symptoms to 5 to 7 days after symptom onset), whereas the likelihood of SARS-CoV-2 detection decreases in the second week after symptom onset.

For Antibody tests:

- o In contrast to RNA and antigen detection, immunological responses take longer to appear, with antibodies (IgM followed by IgG) typically beginning to appear 6 days after symptom onset, as viral RNA levels begin to decline.

Storage, Packaging and transport of specimens-ICMR guidelines should be strictly

followed to prevent deterioration and contamination of the samples and for the safety of the personnel handling the samples.

5. Commonly used test for diagnosis of COVID-19:

- 5.1. Real Time, Reverse Transcription PCR (RT-PCR) based assays:
 - o This is the **gold standard** and most widely used **Nucleic acid amplification test** (NAAT) for the detection of SARS-COV-2 RNA from Patient samples.
 - o Many commercially available RT-PCR assay kits are available in the market with highly variable sensitivity and specificity; selection of highly sensitive, specific, and **ICMR validated assays** is most crucial for the accurate diagnosis of COVID-19 infection.
 - o The test is based on **the principle of Polymerase Chain Reaction or PCR** - a very sensitive technique which can amplify (produce millions of copies) and detect a single copy of the specific genomic sequence [Fig.4] (Pls. see Color pages section). It uses a mixture of chemicals, enzymes and nucleotides and is carried out in a machine called thermal cycler. Real time, Reverse Transcription-PCR works on the same principle but has an additional step of conversion (**reverse transcription**) of the Viral RNA into complimentary DNA (c DNA), which is then amplified [Fig.5](Pls. see Color pages section). It is a semi quantitative technique as the number of copies of c DNA generated in the RT-PCR increases exponentially and is proportional to the amount of starting material, i.e. viral load. The term "**Real Time**" denotes the fact that results are recorded as the amplification process is still on going by measuring the emitted fluorescnce, whereas conventional RT-PCR only provides results at the end of the process.
 - o Most RT-PCR assays specifically detect **2 to 3 specific gene segments/targets** in the SARS-COV-2 viral RNA genome, eg. E, N, S, ORF1ab, RdRp. According to the WHO

- guidelines, in order to confirm the diagnosis, a validated RT-PCR assay targeting a minimum of two regions on the SARS-CoV-2 genome must be chosen.
- o Depending upon the gene target, sequence-specific forward and reverse **primers** (short segments of nucleotides) which bind with specific gene segments and a fluorogenic probe are designed and utilized in real-time RT-PCR diagnostics
 - o Viral RNA, when present is first **extracted** from the biological specimen collected and then **purified**.
 - o Purified viral RNA template is **converted into a cDNA** (complementary DNA) by an enzyme called **reverse transcriptase** (an RNA-dependent DNA polymerase enzyme).
 - o Specific gene targets when present are subsequently amplified by PCR
 - o During amplification, the fluorescence signals are detected in real-time and the fluorescence emission data is plotted against the replication cycles.
 - o **The cycle threshold (Ct) value for a the gene target** is determined by the number of PCR cycles needed to report a detectable fluorescence, i.e. greater than the baseline fluorescence. Therefore, a lower Ct value implies the presence of a greater initial viral RNA load in the specimen and vice-versa.
 - o In general, for diagnosis of COVID-19 infection, globally the accepted cut-off for Ct value for Covid-19 ranges between 35 and 40, depending on performance characteristics of the different assays. The ICMR has arrived at the Ct value of e"35 based on laboratory experiences and inputs taken from several virology labs.
- Other RT-PCR based assays:**
- o **High through put RT PCR based systems:** Automated assays with a capability to process 1000 to 3000 samples/day
 - Abbott RealTime SARS-CoV-2 /m2000 assay
 - COBAS 6800/8800 SARS -COV-2 assay
 - o RT-PCR based Rapid diagnostic tests:
 - **CBNAAT**-FDA approved ,Cartridge Based Nucleic Acid Amplification Test (CBNAAT) using Cepheid Xpert Xpress SARS-CoV2 assay
 - **TRU NAT**(Mol bio diagnostics,India)-indigenously developed microchip based assay
- Interpretation of RT-PCR results:**
- **Positive test result:** A positive PCR result means that the person the sample is currently infected by the virus.
 - A negative PCR result could be due to any of the following:
 - the person is not currently infected by the virus
 - the virus is not present at the site the sample was taken from
 - the sample taken was of poor quality
 - sample was taken too early, or too late in the infection to detect replicating virus.
 - Technical problems during performance of the assay.
- When COVID 19 is strongly suspected but RT-PCR is negative, the test has to be repeated after a few days to reduce the chance of incorrectly missing an infected person.
- Advantages:**
- Universally recommended Gold standard test with Good sensitivity and excellent specificity **for COID-19 diagnosis.**
 - Availability of the **highly sensitive, commercial, RT PCR based Rapid Diagnostic tests (RDT)**-These are successfully being used in Remote areas with no modern laboratory infrastructure or trained personnel.
 - Availability of **High throughput RT-PCR based systems** capable of processing large numbers of samples in a short period.
- Limitations :**

- Trained personnel, specialized Infrastructure and equipment required for RT-PCR lab.
- **False negative results**, when performed on samples with low viral load, including swabs taken incorrectly or obtained from asymptomatic or mildly symptomatic patients, or obtained too early or too late. In one study RT-PCR done on upper respiratory tract samples reported a false negative rate of 38% on the day symptoms appeared. It dropped to 20% on the third day after symptom onset but rose to 67% about two weeks later.
- **Contamination and interference:** RT PCR assay may be affected by contaminants and interfering substances contained in the sample or introduced by the operator. To avoid reporting false positive or false negative results, WHO recommends that each RT-PCR run should include both external and internal controls, and also encourage laboratories to participate in external quality assessment schemes.
- **Long Turn around time (6-8hrs)** with non automated lab based assays, can take up to 24 h to obtain a result that can be communicated to the patient.
- **Preanalytical and analytical factors**-RT-PCR is a method that is profoundly affected by factors such as collection, storage, shipping and handling of samples, and technical expertise.
- s **Possible decreased sensitivity** when the sample contains SARS-CoV-2 genomic variants. Molecular tests designed to detect multiple SARS-CoV-2 genetic targets are less susceptible to the effects of genetic variation than tests designed to detect a single genetic target.

5.2. Antigen detection Tests/rapid Antigen tests (RAT)

- o They detect SARS CoV 2 protein antigens (Nucleocapsid (N) or Spike(S) protein antigens) in swabs collected from the upper airways of the subject with suspected active COVID 19 infection.

- o These Rapid antigen tests (RAT) are mainly built on platforms based on the principle of lateral flow immunoassay (LFIA).
- o The principle behind these LFIA rapid antigen tests is based on the bond between SARS-CoV-2 protein antigens and the antibodies that occur on the surface of a porous Nitrocellulose membrane where the sample in buffer flows by capillary action[Fig 6]-
- When the specimen is added onto the sample pad of a test cassette, SARS COV2 antigen in the sample binds with colloidal gold-labeled SARS-CoV-2 antibody to form an antibody-antigen (Ab-Ag) complex.
- The Ab-Ag complex is captured by SARS-CoV-2 antibody (Rabbit monoclonal antibody) when migrating to the test line under capillary action. A red- colored band will appear on the test line, which indicates the specimen is positive for SARS COV2 antigen. No color band will appear on the test line if the specimen does not contain any SARS-CoV-2 antigen, or the antigen level is below detection limit.
- A colored band on the control line represents the proper liquid flow through the cassette; the absence of a colored band on the control line indicates insufficient sample or buffer volume and the test is considered Invalid.

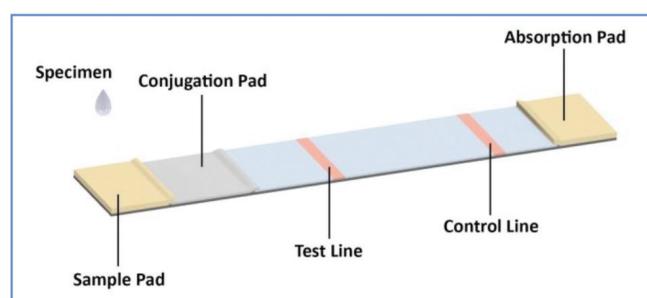


Fig 6: Principle of Lateral Flow Immuno Assay (LFIA)

Interpretation of RAT Results:

- o **POSITIVE:** A colored band appears on the control line (C line), a second colored band shows up on the test line (T line). A positive result indicates the presence of COVID- 19 antigen in the patient sample denoting an

active infection.

- o **NEGATIVE:** A colored band appears on the control line (C line); no colored band shows up on the test line (T line). A negative result indicates there is no coronavirus antigen in the specimen, or the level of coronavirus antigen is below the detection limit.
- o **INVALID:** No colored band appears on the control line (C line). An invalid test result suggests there might be insufficient buffer volume or incorrect operating procedures. Carefully review the test procedure and test the same patient again with another coronavirus antigen rapid test cassette. Contact the kit distributor if the problem persists.

Advantages:

- o produce results faster than NAAT
- o Potential use as point-of-care tests; can be done on location reducing the burden on the testing laboratories.
- o yield results in as little as 15 to 20 minutes.
- o less expensive compared to NAAT and don't require specialized laboratory technique, equipment or trained personnel
- o offers quick screening and detection of COVID-19 among high-risk groups and in high-congregate environments (such as prisons and long-term care facilities).

Disadvantages :

- o **Low sensitivity i.e. more false negative results**-a Cochrane systematic review of 22 antigen test studies found highly variable sensitivity among kits with an average sensitivity of 56.2%. The specificity was good around 99.5% indicating less false positive results.
- o When COVID 19 is suspected, **A negative RAT test should be followed up with a RT-PCR test** as samples with low viral loads may be missed. Greatest utility may be in symptomatic patients, when the viral load will be at its greatest, to enable accurate triage.
- o **Less expert interpretation in point-of-care**

settings. Although point-of-care testing is convenient, it is important to remember that the test is often performed and interpreted by healthcare professionals that are not trained in clinical laboratory science; the possibility of false negative and false positive results should be emphasized and use of public health measures, such as masking and distancing should be continued to prevent transmission.

5.3. Serological Immuno assays for the detection of SARS-CoV-2 specific antibodies:

- o have limited utility for the diagnosis of COVID-19 in the acute stages of the illness as time required to detect immune responses to SARS-CoV-2 is around 1 to 2 weeks[Fig.3]
- o The median seroconversion times for total antibody, IgM, and IgG were 9, 10, and 12 days after symptom onset (or 15, 18, and 20 days after exposure), respectively.
- o Samples used: serum is most commonly used; plasma, or whole blood (including fingerstick and heel pricks also used , and the possibility of antibody detection in other body fluids such as saliva is being explored .
- o Many serological assays for antibody detection have been developed and commercialized and mostly are based on Enzyme linked Immuno Assay(ELISA),Chemiluminescence Immuno assays(CLIA)and LFIA platforms .
- o these use recombinant antigens to capture SARS-CoV-2-specific antibodies, with the **N protein** and the **receptor-binding domain (RBD) of the S1 subunit of the S glycoprotein** being the most commonly used antigens.
- o Serological methods can target one or more immunoglobulin isotypes (i.e., IgA, IgM, or IgG) or total antibody.

Interpretation of antibody testing results-

- **Positive-**

indicates the individual had previous symptomatic or asymptomatic infection with SARS-COV-2 or received Covid vaccine.

- **Negative-**

The Individual did not have covid-19 in the past and was not vaccinated. [Note: a small proportion of individuals who had Covid infection or received Covid vaccine may never develop antibodies.]

Test will be negative if patient has a current infection, been recently infected, or been recently vaccinated; It typically takes 1 to 3 weeks after infection or vaccination to have detectable levels of antibody.

Applications :

- to determine past exposures of populations to SARS-CoV-2 (e.g., sero-surveillance in health care workers or the general population),
- for use in seroprevalence studies to aid in ongoing outbreak investigations (to identify cases beyond the detectable window of NAATs)
- as an adjunct to molecular testing to support the identification of SARS-CoV-2 in a patient suspected of having COVID-19 (i.e., persistent or progressing symptoms) but with repeat negative results obtained by NAATs.

Advantages:

- Antibody testing can identify previously infected individuals who are asymptomatic. This information is essential for guiding transmission control measures such as quarantine, isolation, and social distancing, as well as the closure of schools, places of worship, and businesses.
- Another benefit of antibody testing is that it can aid in vaccine development and efficacy. The testing can identify which parts of the virus the immune system responds to and should be targeted during vaccine development.

Disadvantages:

- **Some individuals don't develop detectable IgG or IgM antibodies** after infection or vaccination; so the absence of detectable antibodies doesn't rule out a previous COVID-19 infection.

- **The correlation of antibody levels with immunity is uncertain and is being studied:** Testing positive for IgG antibody after natural infection or vaccination often did not protect patient from reinfection. Also some individuals may not have detectable levels of antibodies but that does not preclude memory B cell activity or functional T cell mediated immunity to COVID-19.
- Lack of standardization and Variable performance of the available tests makes test interpretation complex.

Virus neutralization assays-

- Essential to functionally measure antibody inhibition of SARS-COV-2 infection, which is remains a major gap when using the available antibody assays.
- Plaque reduction neutralizing test (PRNT)- is the gold standard Neutralization assay but due its low throughput ,is not practical for large scale use.
- High throughput assays for eg. fluorescence based assays are being developed as a rapid platform to screen people for antibody protection from COVID-19,for evaluation of vaccine efficacy.

5.4. SARS-CoV-2 Next-Generation sequencing (NGS)-

- NGS is an emergent technology that has the power to sequence billions of nucleic acid fragments simultaneously, with recent advances rendering dramatically reduced time and cost of sequencing.
- NGS was used to identify the novel coronavirus causing COVID-19 early in the outbreak.
- Illumina's next-generation sequencing (NGS) test for COVID-19 was the first to be authorised for NGS based diagnosis of Covid-19.
- Several challenges need to be addressed before NGS can be adopted for routine diagnostic use.
- NGS continues to provide public health

officials, vaccine and drug developers, and researchers with critical evidence, allowing labs to:

- Track the transmission routes of the SARS-CoV-2 globally
- Detect mutations quickly to prevent the spread of new variants of the Virus
- Identify viral mutations that can avoid detection by established molecular diagnostic assays
- Identify viral mutations that can affect vaccine potency
- Screen targets for possible COVID-19 therapeutics
- Identify and characterize respiratory co-infections and antimicrobial resistance alleles

5.5. Viral Culture-

- **Not recommended for routine laboratory Diagnosis of COVID 19-** due to the Long Turn around time, Biosafety concerns and requirement for trained personnel, equipment and infrastructure.
- Isolation of Viral strains is required for research in the following areas
 - Antivirals
 - Vaccine development
 - Pathogenesis
 - Viral stability

6. Common controversies and challenges in laboratory testing for COVID-19:

- a) The role of follow up RT-PCR testing in defining the duration of isolation/quarantine and for discharge from hospital:

Studies have shown that some patients continue to test RT-PCR positive for weeks to months after resolution of symptoms. Earlier 2 consecutive negative RT-PCR tests were necessary as per CDC guidelines to discharge a patient from the hospital, leading to prolonged hospitalization, loss of work, psychological stress and continued use of PPE.

The Current opinion is that **follow up RT-PCR testing is not necessary** and should not be used as "test of cure" following an initial diagnosis of COVID-19 to determine whether an individual continues to shed infectious SARS-CoV-2. U.S. CDC no longer recommends the use of a SARS-CoV-2 test-based strategy to determine when to discontinue transmission-based precautions, instead relying on a symptom-based strategy in the majority of situations.

Revised discharge policy released by the MoHFW, GOVT. OF INDIA also endorses the same view. Repeat molecular testing may be indicated in patients who recover and subsequently develop new COVID-19-related symptoms.

The rationale is that molecular tests cannot differentiate between non- infectious fragments of viral nucleic acid persisting in the cells from an infectious Virion. Bullard et al have demonstrated that Viral cultures from patient samples turn negative by an average of 8 days following symptom onset, even though RT-PCR continues to remain positive.

- b) Whether Cycle Threshold(Ct) value should be provided in the RT-PCR test report.

The Ct value is inversely proportional to the amount of target nucleic acid and can be used as a relative indicator of the concentration of the Virus in a clinical specimen. For

e.g. Ct value of 15 would indicate a very high concentration of the target nucleic acid in a sample while a Ct value of 35 may indicate a low concentration. But several studies have shown that the Ct value is dependent on a number of variables, including the assay's gene target, the extraction platform, PCR amplification chemistry, the timing of the sample and even the quality of specimen collection. Till further supporting evidence is obtained ,as per the current opinion, the **Ct value should not be routinely reported**. On a case-by-case basis, the CT value may be provided (i.e., verbally) to the ordering physician upon request. This approach allows for clarification of the assay used for testing

and a discussion of the limitations associated with using the CT value while interpreting the result.

- c) Value of SARS –COV-2 antibody tests in evaluating a person's level of immunity or protection after COVID-19 vaccination or infection.

Currently the available SARS-CoV-2 antibody tests have not been found to be useful to assess the level of protection provided by an immune response to COVID-19 vaccination. If antibody test results are interpreted incorrectly, there is a potential risk that people may take fewer precautions against SARS-CoV-2 exposure thereby increasing their risk of infection and further spread. Viral neutralization assays under development may fill this gap.

- d) Performance of RT-PCR based assays in detecting the emerging SARS-CoV-2 variants-

International and national regulatory agencies like FDA, ICMR regularly monitor the performance of the approved RT-PCR assays for the detection of SARS-CoV-2 variants and issue alerts to health care providers. Performance of some RT-PCR tests may be potentially affected in the presence of SARS-CoV-2 genetic variants, if the mutation or change in the Viral genome affects the gene target which is being detected by the RT-PCR Assay. This may lead to false negative results. **As most approved RT-PCR assays detect multiple gene targets, the overall test sensitivity is not affected while detecting variant strains.**

7. Conclusion:

Since the recognition of the novel corona virus SARS –COV-2 in January 2020, tremendous efforts have been made to develop highly accurate tests for the diagnosis of COVID-19.

Knowledge of the various diagnostic tests is still evolving and innovative technologies that have the potential to accelerate SARS-CoV-2 detection in the future, including digital PCR, CRISPR and microarrays are under various stages of development and validation. A clear

understanding of the nature of the tests, interpretation of their findings, their advantages and limitations is necessary, as rapid and accurate laboratory diagnosis is crucial to containing and mitigating the COVID -19 pandemic.

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Inflammatory Markers in COVID 19

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INTRODUCTION

COVID 19 pandemic has caused significant mortality and morbidity across the world. Even though the pandemic began 18 months ago, many countries are still experiencing second and third waves putting significant constraints on health care systems. Principles of management of COVID-19 involves early diagnosis, triaging high-risk patients, antivirals and immunomodulators in suitable patients and supportive therapy. Routine investigations help clinicians in multiple ways to assess the severity of the disease, prognostication, early initiation of medications and predictors of mortality.

Biomarkers are defined as "Objectively measured and evaluated as an indicator of normal biological and pathological processes, pharmacological response to a therapeutic¹". In this chapter, biomarkers and inflammatory markers are used interchangeably.

ROLE OF BIOMARKERS

- (i) Early suspicion of disease
- (ii) Confirmation and classification of disease severity
- (iii) Framing hospital admission criteria
- (iv) Identification of high-risk cohort
- (v) Framing ICU admission criteria
- (vi) Rationalizing therapies
- (vii) Assessing response to therapies(viii)
Predicting outcome
- (ix) Framing criteria for discharge from the ICU and the hospital

Inflammatory markers help clinicians identify patients at risk of deterioration, especially those working in primary care settings, resource-limited

settings, so that patients can be referred to higher centres at the earliest. However, to date, no single inflammatory marker has helped clinicians decide on treatment. Multiple studies have attempted to create clinical scores by combining multiple inflammatory markers to predict prognosis. These markers are less expensive, turn over time is fast and are readily available in labs.

There are several limitations of these biological markers. Inflammatory markers should not be used for diagnosis of COVID19 because these are not disease-specific, represent host response to infection. Levels of Inflammatory markers are dynamic and influenced by the disease's timeline, severity, host immunity, and immunosuppressive therapy. COVID 19 is not a local respiratory disease but a multisystem disease involving the interplay between immunological, inflammatory systems. COVID 19 stimulates both innate and adaptive immune systems. Dysregulated immune response and excess proinflammatory response leads to sepsis and organ dysfunction.

Many inflammatory markers are abnormal in COVID 19; the most commonly used markers are C-reactive protein (CRP), ferritin, lactate dehydrogenase, interleukin 6 (IL 6), procalcitonin, creatine kinase (CK). Interpretation of these markers requires understanding their dynamics and limitations. Rather than relying on a single biomarker value, serial measurements help us better understand the disease progress.

The use of these biomarkers in understanding COVID-19 may also help to prevent virus-induced acute inflammatory response complications such as acute hypoxic respiratory failure and multiorgan dysfunction, including acute cardiac, hepatic and renal injury in affected patients. Biomarkers like procalcitonin help us to effectively initiate and stop

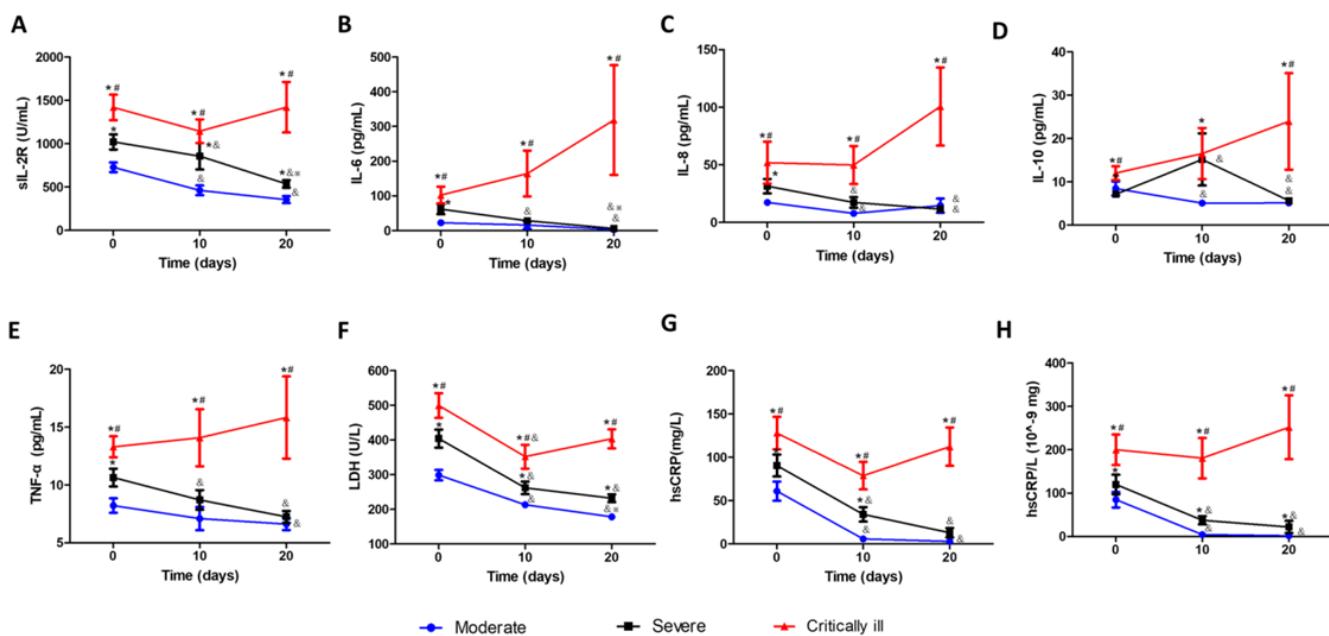


Figure 1: Inflammatory parameters in COVID19 with different disease severity²

antibiotics in COVID 19 patients with a secondary bacterial infection. Antibiotic treatment decision making based on biomarkers like procalcitonin has been found to be very effective.

C-reactive protein (CRP)

For many decades CRP has been used as an acute-phase protein for inflammation and tissue damage. Its name was derived because of its ability to precipitate somatic C polysaccharide of streptococcus pneumoniae. Hepatocytes produce CRP. CRP is secreted in response to IL6 stimulation.CRP plays a crucial role in innate immunity.CRP's function involves activating the classic pathway complement system, binding to the Fc receptor, leading to proinflammatory cytokines.

CRP levels increase within 6 hrs after inflammation and reach peak concentration by 48 hrs, and levels decrease by 48 hrs. CRP levels decrease rapidly with resolution of inflammation. For this reason, CRP is a handy clinical tool for evaluating infection and monitoring response to therapy and prognosis. Elevated CRP levels are directly correlated with the level of inflammation and disease severity. Normal serum levels are less than 3 mg/dl. Even though serum levels can be increased in infection and inflammation, it can also be increased in trauma, necrosis(myocardial infarction), malignancy (lymphoma).

CRP as an inflammatory marker in COVID 19 patients has been extensively evaluated. Clinicians have used CRP as a marker for prognostication, response to therapy. CRP values of more than 10 mg/dl has a four-fold increased risk of poor prognosis. Similarly, survivors had a 40mg/dl median value in a study, while non-survivors had 125mg/dl. High CRP values at admission have been associated with a poor prognosis. CRP is a more effective and sensitive biomarker than neutrophil lymphocyte ratio (NLR), ferritin, LDH, IL-6 and CK in predicting disease progression.

'Rule-of-6' involving CRP, ferritin and lactate dehydrogenase (LDH) measured in the first 48 hours of admission which identified patients at risk of disease progression: A first 48-hour "Rule-of-6": using ferritin >600 μ g/L, LDH >600U/L and CRP >60 mg/L to aid early identification of COVID patients at risk of disease progression.²

Effect of COVID19 treatment of CRP levels: Anticoagulation leads to a reduction of both D-dimer and CRP levels. Similarly, administration of corticosteroids and immunnosuppressive drugs like tocilizumab significantly reduce CRP levels independent of clinical condition. Withdrawal of steroids will have a rebound effect on CRP levels. These effects can confuse clinicians and lead to excess use of immunosuppressive drugs and antibiotics.³⁻⁶

Interleukin 6 (IL-6)

Interleukin 6 is a cytokine produced in response to infections and tissue damage. The biological consequences of IL-6 are both pro-and anti-inflammatory effects. IL6 connects innate and adaptive immunity by promoting the differentiation of naïve CD4 cells. It has a vital role in controlling viral infections. Macrophages and T lymphocytes produce IL6.

IL6 levels are elevated in response to tissue injury and infection. The average serum level of IL6 is <1.8 pg/dl. IL6 is very unstable. Serum levels may vary significantly if not immediately frozen or refrigerated. High levels of IL6 in COVID 19 patients have been associated with severe disease. High IL6 levels have been reported to be superior to CRP and other inflammatory markers in predicting organ dysfunction. IL6 levels of more than 24pg/dl is a good screening tool.

High IL6 levels during COVID 19 infections have therapeutic implications. Several studies have published the effect of Anti-IL6 agents (e.g. Tocilizumab) on COVID 19 outcomes. The outcome of these studies was mixed. These studies did not categorize the patients based on IL6 levels; instead used hospital protocols to recruit the subjects, which could explain the outcome. IL6 levels should be monitored not only at admission but throughout the disease, and patients with rising levels should be initiated with anti-IL6 agents before clinical deterioration. The level above which clinical deterioration is expected has not been determined, but many studies have suggested that patients having levels above 86 pg/dl are likely to deteriorate rapidly.⁷

Procalcitonin (PCT)

Procalcitonin, as the precursor of calcitonin, is a kind of glycoprotein without hormone activity, which is significantly higher in bacterial infection, but remains normal or slightly increased in viral infection. Procalcitonin has been used as an early marker of sepsis. PCT has high specificity in differentiating bacterial and non-bacterial sepsis⁸. PCT as a biomarker will guide us to initiate and stop antibiotics. PCT is sensitive marker for bacterial sepsis as it undergoes downregulation in viral

infections, unlike WBC counts and CRP. Circulating endotoxins are the trigger for PCT synthesis. PCT can also be stimulated by IL6, TNF alpha, IL1b.

PCT is detected within 4 hours after the onset of infection and peaks at 6-12 hours. The half-life of PCT is 24 hrs. The kinetic profile makes PCT ideal for diagnosis and monitoring of the infection. The average value of PCT is less than 0.05 ng/L. A value more than 2ng/L is suggestive of systemic infection, and a value of more than 10 ng/L is highly suggestive of severe systemic bacterial infection. Apart from bacterial infection, PCT can be increased in severe burns, pancreatitis, severe trauma, renal failure, recent major surgery. However, in these conditions, serial values will decrease in the absence of bacterial infections.

In a meta-analysis of COVID 19 patients, elevated PCT >0.5ng/dl was associated with a five-fold risk of poor outcomes. PCT may remain within normal limits, but a continuous increase in PCT levels may indicate a bacterial co-infection and progression towards more severe complications such as COVID-19 pneumonia and acute respiratory distress syndrome (ARDS).⁸

Erythrocyte Sedimentation Rate (ESR)

ESR is a non-specific inflammatory marker seen increased in various conditions. ESR levels are found to be elevated in covid 19. Higher levels of ESR were seen in patients with severe covid cases in a study by J Wang et al. Mean ESR levels in severe cases was 36.8 ± 13 mm per hour. Other ventilator-dependent cases had higher ESR than the cured ones (36.8 ± 13 vs 7.2 ± 9.6 mm per hour). ESR may be affected by various factors like age, sex and haemoglobin levels. Hence, these factors should be considered before considering ESR as a sole marker of inflammation in Covid 19 cases.⁹

Lactate dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is an enzyme that metabolizes lactate to pyruvate in the cells of most body tissues. Serum LDH levels are increased following tissue breakdown. Elevated serum LDH is seen in several clinical conditions like hemolysis, cancer, severe infections, sepsis, liver diseases and hematologic malignancies. Serum LDH is seen

elevated in covid 19 cases. In a meta-analysis of studies in an Asian population, the authors showed that serum LDH was higher in severe cases than mild to moderate cases with a weighted mean difference of 102 IU/L. A serum LDH of >245 IU/L was seen in severe covid cases in a study in the Chinese population.^{10,11}

A study by Wu MY et al demonstrated the importance of serial measurement of LDH. An increase in serum LDH values by 62 IU/L showed a significant correlation with radiological worsening. Also, the time of LDH normalization on recovery correlated with radiological improvement. Similar results in a study by Kogan D et al prompted the authors to suggest higher serum LDH levels as an indicator for computed tomography scan of covid 19 patients.^{12,13}

Ferritin

Serum ferritin is an indicator of body iron stores. It is elevated in a wide array of diseases like autoimmune, haematological and inflammatory diseases. The role of elevated serum ferritin in Covid 19 has been studied widely. The increase in serum iron and ferritin is a consequence of damage to haemoglobin from novel coronavirus, which may lead to reactive oxygen species-mediated organ damage and hypercoagulability. A possible source for serum ferritin is from the liver and macrophages. In a study by Qaedan F et al , serum ferritin value of >714ng/ml was associated with increased mortality. A value of >502ng/ml was associated with ventilator dependence. In a systematic review and meta-analysis, a serum ferritin value of >307ng/ml was associated with severe covid 19.¹⁴⁻¹⁶

D-dimer

D-dimer is one of the end products of the coagulation cascade. Many studies in the literature have proved its role in the diagnosis of venous thromboembolism (VTE). Pulmonary immunothrombosis plays a major role in Covid-19 disease progression. This has been demonstrated on autopsy studies on covid 19 patients, demonstrating both micro and macrovascular pulmonary thrombosis. Hence D-dimer plays a role of a potential diagnostic marker of thrombosis in covid 19.¹⁷ In a retrospective analysis by Yu HH et

al, D-dimer value of >0.5µg/ml was seen in severe covid 19 disease compared to mild cases, with a median value of 1.8µg/ml. A meta-analysis of studies on D-dimer showed that patients with severe covid 19 had d-dimer values which were higher by 0.91 compared to mild cases, and odds of severe infection was associated with D-dimer greater than 0.5 µg/ml (odds ratio = 5.78, 95% confidence interval, 2.16–15.44, $p < 0.001$) on admission. In a meta-analysis by Du WN et al, a higher D-Dimer had 1.9 times odds of developing severe covid. In another study by Duz ME et al, a D-dimer of more than 2.1µg/ml was predictive of severe disease. A higher value of D-dimer is associated with poor prognosis as evidenced by a study in African population by Qualim S et al which showed that a value of more than 1.3µg/ml was predictive of mortality.¹⁸⁻²⁰

D-Dimer levels are not always associated with venous thromboembolism. It's a non-specific marker that is elevated in various conditions like disseminated intravascular coagulation, sepsis, liver diseases and malignancy. Hence it serves as a good marker in excluding the diagnosis of VTE. Current data do not support the routine use of high D-Dimer levels in isolation to guide decisions regarding investigation and anticoagulation. D-Dimer levels should be assessed within the overall clinical context and, if markedly elevated, may prompt investigations to exclude VTE.

Take home points:

- Biomarkers or inflammatory markers aid in the diagnosis and assessment of severity of Covid 19
- Serum ferritin >600 µg/L, LDH >600U/L and CRP >60 mg/L, "the rule of 6" identifies Covid patients at risk of disease progression.
- D-dimer has a high negative predictive value to rule out VTE in covid 19 patients.
- Serum procalcitonin >2µg/L may suggest secondary bacterial infection in Covid 19 patients.
- Periodic measurement of markers in combination aids in assessing disease progression or recovery.

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Imaging in COVID-19



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ABSTRACT:

SARS-CoV-2 is a novel coronavirus that has rapidly resulted in a worldwide pandemic and has been the cause of extreme morbidity and mortality. It primarily affects the respiratory system but has also been shown to impact other systems in the human body, resulting in multiorgan injury and, in some cases, failure. Imaging plays a significant role in the detection, diagnosis, and assessment of virus-induced injury and associated complications. Recognizing and understanding the pathophysiology of the virus and its effects on the immune system and coagulation is paramount toward improving radiologists' ability to accurately identify key imaging findings and promptly recognize possible complications, thus minimizing the number of diagnostic misinterpretations. Owing to the complexity of viral pathophysiology and its targeting of multiple organ systems, the recognition of one complication should prompt intense scrutiny for others, particularly if patients are critically ill.

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The diagnosis of COVID-19 is currently confirmed by laboratory testing through identification of viral RNA in reverse transcriptase polymerase chain reaction (RT-PCR).

It has become apparent that although COVID-19 predominantly affects the respiratory system. COVID-19 manifests with non-specific respiratory symptoms of variable severity and may require advanced respiratory support. But most of the

times COVID-19 typically presents with systemic (multiple organ dysfunction, MODS-SARS-CoV-2) and/or respiratory manifestations. Some also experience mild gastrointestinal or cardiovascular symptoms, although these are less common. Others may present solely with a gastroenteritis-like illness, which may not initially be recognized to be COVID-19. A significant minority of individuals infected with SARS-CoV-2 remain asymptomatic throughout the course of their illness. Children seem to be relatively unaffected by this virus, or indeed other closely-related coronaviruses. In a small proportion of the patients however a severe, delayed complication termed multisystem inflammatory syndrome in children (MIS-C) can develop, which is characterized by systemic shock with multi organ involvement. Symptoms and signs are non-specific.

So the full spectrum of clinical manifestations of COVID-19 is broad. Knowing about multisystem imaging findings of coronavirus disease is very important in patient's clinical management.

PULMONARY MANIFESTATION OF COVID-19 DISEASE AND IMAGING MODALITIES:

Chest imaging has been considered as part of the diagnostic workup of patients with suspected or probable COVID-19 disease where RT-PCR is not available, or results are delayed or are initially negative in the presence of symptoms suggestive of COVID-19. Imaging has been also considered to complement clinical evaluation and laboratory parameters in the management of patients already diagnosed with COVID-19. Imaging may be considered to triage patients in the resource-constrained environment as recommended by the Fleischner Society expert statement

The guidelines and recommendations for imaging in Covid19 disease, have been ever changing since the beginning of Pandemic in December 2019. What started as obtaining only Chest Radiographs in the early stages has shown a complete paradigm shift towards performing HRCT chest for evaluation of lung lesions and occasionally in the course of disease on more than two occasions. Recently, POCUS (Point of Care Ultra sound) is also incorporated for regular bedside follow up evaluations.

As the diagnostic techniques for COVID-19 continue to evolve, laboratory confirmation of COVID-19 remains the initial screening test of choice with a limited role of CT chest in diagnosis or screening. A variety of chest imaging findings have been described in patients with COVID-19. No study evaluated the diagnostic accuracy of chest imaging in asymptomatic patients possibly infected with SARS-CoV-2. In symptomatic patients in high COVID-19 prevalence cohorts, chest computed tomography (CT) appears to be associated with high sensitivity but low specificity, resulting in weak positive likelihood ratios and stronger negative likelihood ratios. This indicates that in these settings, negative imaging findings might be useful for ruling out COVID-19. The ACR, CDC, RSNA, and STR at this point do not see the advantage of screening CT as it is non-specific and will not change management and quarantine status, which is dictated by the patient's history and symptoms. Initial CT chest can be negative in up to 25% of patients with COVID-19. However, sensitivity increases with disease progression with abnormal findings in 95% of cases after 5-6 days of infection. CT chest should only be performed if there is a clinical indication for it in accordance with ACR appropriateness criteria for acute respiratory illness in immunocompetent patients. CT chest may also be considered for evaluation of complications as superimposed bacterial pneumonia, abscess, or empyema.

Evidence on the diagnostic accuracy of chest x-ray (CXR) was very limited, but suggests lower sensitivity and possibly higher specificity than chest CT for diagnosing COVID-19.CXR appears to be a reasonable imaging modality of choice in patients

with suspected and pending RT-PCR for COVID-19.In hospitalized patients, CXR remains the imaging modality of choice as a baseline imaging and monitoring disease progression and complications.

Point of care lung ultrasonography for the diagnosis of COVID-19 remains an investigational tool and is currently not recommended as a diagnostic test by major professional imaging societies. Evidence on the diagnostic accuracy of lung ultrasound (LUS) was limited to one study that used chest CT findings as the reference standard.

IMAGING FEATURES OF COVID-19 ON CHEST RADIOGRAPH

Chest radiography is typically the first-line imaging modality performed in patients with suspected COVID-19 infection.

Chest imaging findings of SARS-CoV-2 infection overlap with or mimic those of other infections, including those caused by other human coronaviruses (severe acute respiratory syndrome

Coronavirus, or SARS-CoV; Middle East respiratory syndrome coronavirus, or MERS-CoV); influenza A virus, or H1N1, and other influenza viotypes and acute lung injuries from drug reactions and connective tissue diseases.

Findings of COVID-19 on chest radiographs vary, ranging from normal in the early stages of disease to unilateral or bilateral lung opacities, sometimes with a basilar and strikingly peripheral distribution. Early research reported a relatively low sensitivity (69%) for the diagnosis of COVID-19 using baseline chest radiography. Although underlying comorbidities such as chronic lung disease or congestive heart failure may confound chest radiograph interpretation, studies have shown that many of the hallmark chest CT findings are apparent on chest radiographs.

The advantages of CXR include portability and easy accessibility.

But the limitation is poor sensitivity in early stage of disease. CXR should not be indicated to rule out COVID-19 infection due to its low sensitivity. A normal CXR does not rule out the possibility of pneumonia in general and does not exclude the

diagnosis of pneumonia in patients with suspected COVID. However, chest radiography is valuable to image the evolution of COVID-19 pneumonia, which can be followed using serial CXR, helping in its management decision pathways both in the Emergency Department and inpatients setting.

Indications for chest radiograph in Covid -19 disease are Initial base line study, for monitoring rapid progression of Disease, for monitoring the progression and later stages of COVID-19, especially in patients in a critical state.

CXR findings Typical of Covid -19 pneumonia are Bilateral poorly marginated opacities especially peripheral mid and lower lung zones (sometimes rounded) Multi focal bilateral consolidations, Diffuse Air space disease / ARDS

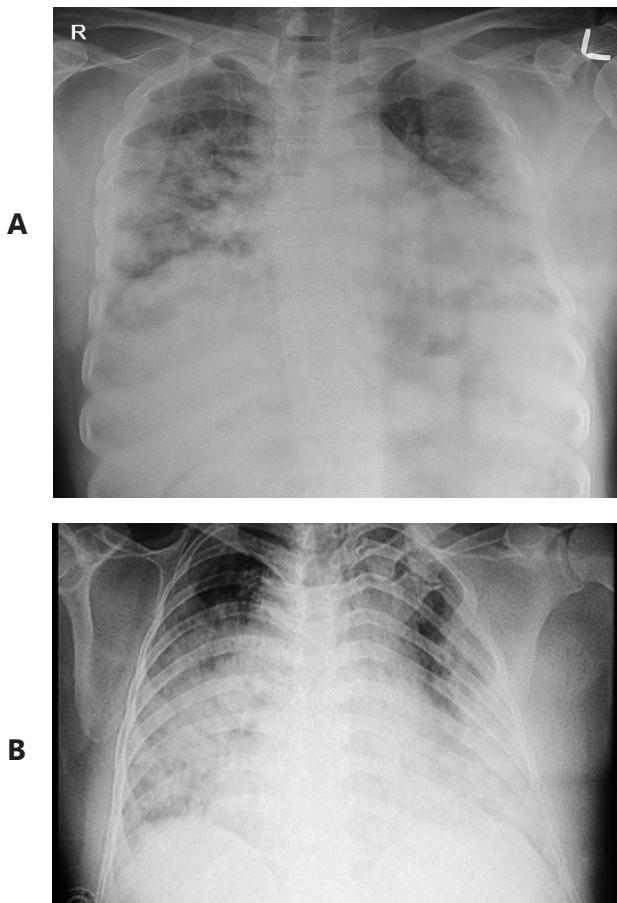


Fig 1.CXR findings of Covid -19 pneumonia: Posteroanterior chest radiograph shows bilateral peripheral and rounded lower and midzone zone opacities (A) and diffuse air space disease (B) in two different patients who has RT-PCR positive Covid -19 disease

Non-specific finding and less typical for Covid-19 disease seen as patchy focal opacity, Lobar or sub lobar pneumonia.

CT Chest Vs Chest X ray: The classical feature of Covid 19 are the ground glass opacities seen in the sub pleural region, especially in the lower lobes. Several studies have concluded that Chest X ray is not useful in the diagnosis of early Covid and can be used only in the follow-up of patients with severe Covid 19 pneumonia to monitor progression. CT scanning has demonstrated excellent sensitivity and should strongly be considered during the pandemic in the initial assessment of COVID-19. This needs to be balanced against the risk of excess radiation with CT, where capacity allows.

ROLE OF HIGH-RESOLUTION CT IN COVID -19 DISEASE

It provides better visualization of the lung parenchyma defining its extent and nature of involvement in Covid 19 pneumonia. For COVID-19, sensitivity and specificity of RT-PCR assays and chest CT continues to be debated indeed. For a large majority, use of CT as a screening tool is actually discouraged, whereas others who recommend it suggest CT be used as a surrogate diagnostic test. Whatever the debate, all agree with the recommendation of using RT-PCR assays as the reference method for diagnosis. "Sensitivity, specificity, negative predictive value, and positive predictive value of chest CT for diagnosing COVID-19 were 90%, 91%, 89%, and 92% respectively". "The sensitivity of CT for COVID-19 pneumonia is debated in the early period of pandemic but was recently estimated to be higher than that of RT-PCR assays with sensitivity of 91% versus 71%, respectively ($P < .001$), and 90% versus 87% ($P = .04$)."

It has been observed that a good number of asymptomatic or mildly symptomatic patients on the HRCT examination show nonspecific findings which do not progress clinically. It has been observed that studies done in the first week of the disease often give a false sense of security under estimating the severity of disease. Similarly, a mismatch has been observed especially in the younger age group population with the lesions or

extent of involvement in the later weeks of disease and the clinical picture-wherein the hypoxia component is often not in proportion with the lung lesions. A converse is observed in the elderly population where relatively lesser involvement of the lung parenchyma often causes significant hypoxia. RT PCR has false negative results in the initial phase of disease. A normal CT scan does not mean no Covid and similarly lesions seen on HRCT may not represent Covid as other diseases may have similar appearance (false negative and false positive).

Common imaging findings: (FIG 2)

1. **Ground Glass opacities:** Increased density of lungs without obscuring vascular margins due to partial displacement of air from alveoli, usually bilateral-peripheral and multi lobar, may have a rounded morphology, Lower lobe (or middle lobe) predominance, Posterior lung zones. Seen both in early phase of disease (with progression of disease Consolidation and septal thickening appear in the areas of GGO) and in the late healing stage it is seen as GGO containing fibrotic band or atelectasis in lung
2. **Consolidation:** Increased density of lungs with obscuration of vascular margins due to complete replacement of air from alveoli by pus / fluid / blood / cells. Can be Peripheral, segmental, sub segmental and multi lobar, Seen with progressive disease or severe disease. Peripherally located triangular shaped areas of consolidation represent infarcts
3. **Crazy paving:** Ground glass opacity with super imposed inter lobular septal thickening. Indicate interstitial inflammation and alveolar damage, may progress to consolidation
4. **Air Broncho gram and airway changes:** Air filled low attenuation bronchi on a background of opaque lung. There may be associated bronchial mucus plugging / bronchiolectasis
5. **Vascular enlargement:** represents hypertrophy of the sub segmental pulmonary vessels increased in size (> 3 mm) particularly in areas with more pronounced interstitial

impairment. Appearance is attributed to vascular wall inflammation and infiltration. This is important imaging finding in Covid pneumonia. (Non Covid -19 pneumonias do not show this finding)

6.

Reticular Pattern and Linear opacification: represents involvement of the pulmonary interstitium. Inter lobular septal thickening and prominent intra lobular lines seen in patients with longer disease course. Cured patients with Covid 19 Pneumonia may continue to show reticular opacities

Less Common or Unusual Findings

1. **Pneumomediastinum / Pneumothorax / Sub cutaneous emphysema:** Uncommonly seen with high CT severity scores. Thought to represent air leaks secondary to high Intra alveolar pressure with subsequent spread of air along the Bronchovascular bundles. High barotrauma rates in patients with coronavirus disease 2019 infection on invasive mechanical ventilation is associated with a longer hospital stay and is a risk factor for higher mortality. Barotrauma risk is particularly important to recognize as these critically ill patients may be managed by staff less familiar with the management of ventilator settings.
2. **Pleural effusion / thickening:** Usually and uncommonly seen in later phase of disease. The presence of pleural effusion is a sign of poor prognosis in Covid 19 Pneumonia
3. **Nodules:** Denote focal air space opacities of less than three-centimeter size, although tree in bud opacities can be seen in Covid 19 Pneumonia presence of nodules should prompt presence of secondary bacterial infection or aspiration
4. **Mediastinal adenopathy:** seen infrequently in Covid 19 patients. Its presence is considered a risk factor for progressive disease. When present with pleural effusion, tree in bud micro nodules, it suggests possibility of a bacterial super infection

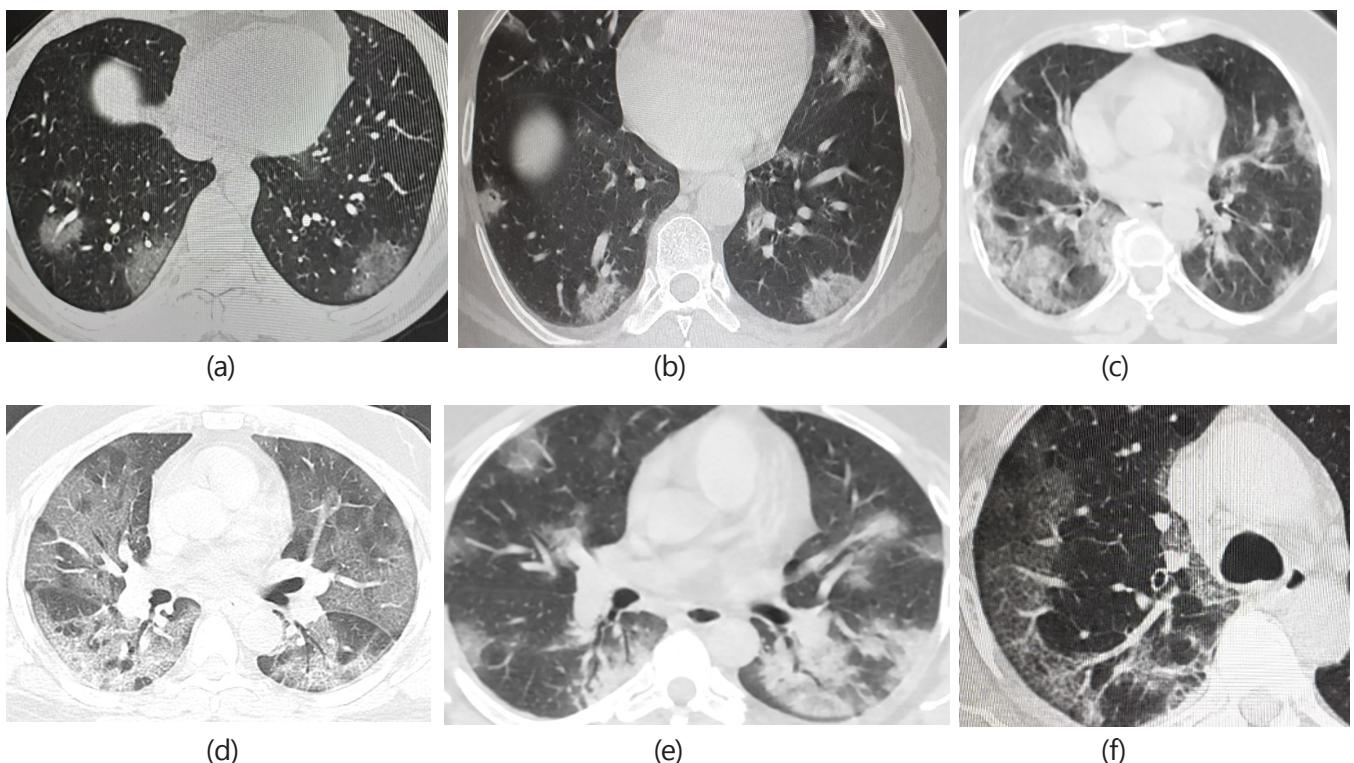


FIG 2. Common HRCT chest findings in a patient with Covid -19 pneumonia: (a) and (b) Axial non enhanced HRCT chest image of 40 yrs old man with covid-19 pneumonia shows multifocal sub pleural areas of Ground glass opacities having a lower lobe predominance. (c)Axial non enhanced HRCT chest image of 54 old females with covid-19 pneumonia shows consolidatory changes in bilateral lung fields mimicking reverse batwing appearance. (d)Axial non enhanced HRCT chest image shows extensive bilateral lower lobe ground glass opacities with associated Inter lobular septal thickening described as the crazy paving pattern. (e) Axial non enhanced HRCT chest image shows air bronchogram within the area of consolidation in a patient with Covid-19 pneumonia. (f) Axial non enhanced HRCT chest image shows enlarged vascular channels in areas of ground glass opacities in a patient with covid-19 pneumonia.

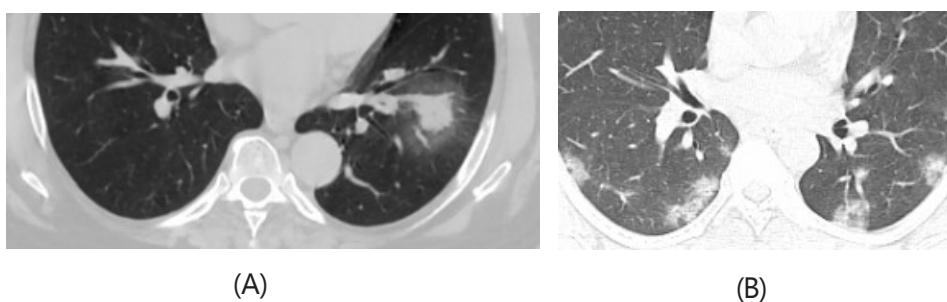


FIG 3. Atypical imaging manifestation of COVID -19 pneumonia: A - Axial CT section of 60 yrs old male patient shows central area of consolidation with surrounding ground glass opacity (Halo sign). B- Axial CT section of CT chest in 59 yrs old female patient shows reverse halo sign /Atoll sign (central ground glass opacity with surrounding consolidation)

5. Atoll Sign: also known as Reverse Halo Sign which is described in Cryptogenic Organizing Pneumonia (COP). It represents an area of central ground glass opacity surrounded by a Ring of consolidation
6. Air bubble sign: Not a specific sign. It denotes presence of a cystic space within the area of air space opacity and thought to represent

expansion of alveolar sacs or bronchioles. It's also described by various other names such as Sieve hole sign and Vacuole sign

Role of CT pulmonary angiography in Covid -19 disease:

Pulmonary Thromboembolism is being increasingly identified in Covid 19 patients with severe Clinical

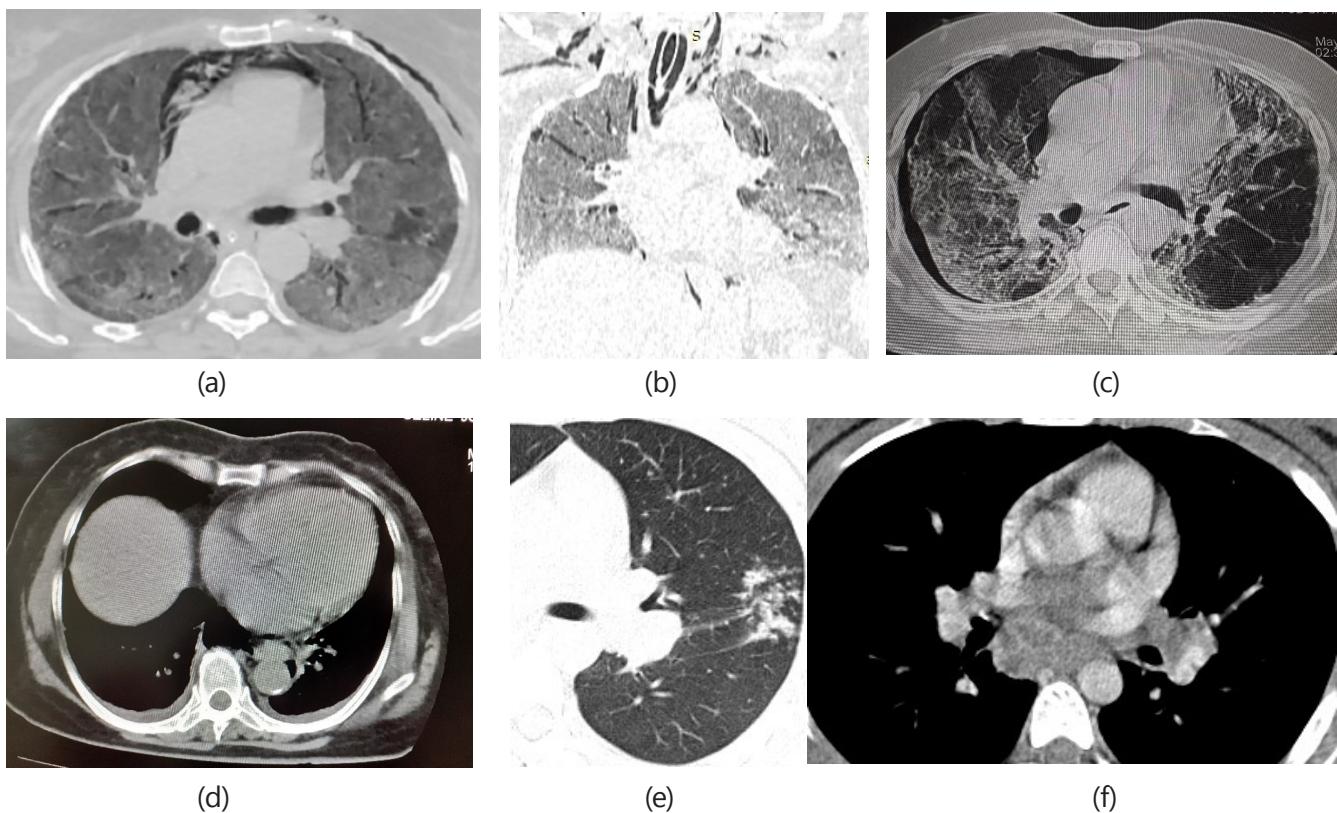


FIG 4. Uncommon HRCT findings of Covid-19 Pneumonia: Fig (a), (b), (c) Axial HRCT chest image shows pneumomediastinum, Subcutaneous emphysema and right sided pneumothorax in a patient with a high CT severity score(d)Axial HRCT image showing minimal bilateral basal pleural effusion and thickening. (e)Axial HRCT image showing small nodular air space opacities (f) mediastinal lymphadenopathy in a patient with Covid -19 pneumonia

features. Frequent association with elevated D-Dimer levels and in patients treated in ICU with mechanical ventilation. Prior to CTPA unenhanced CT scan must be performed. Contrast-enhanced

CT pulmonary angiography is performed to assess for possible PE in patients who develop acute dyspnea or acute deterioration of respiratory symptoms, or those in whom d-dimer markers are significantly elevated.

Table-1 Imaging findings in Covid 19 pneumonia

Common Imaging Findings	Less common or unusual Imaging findings
Bilateral Peripheral ground-glass patches	Central and peripheral ground-glass patches
Multilobe affection	Single lobar affection
Consolidation	Pneumomediastinum / Pneumothorax/ Subcutaneous emphysema
Crazy paving	Pleural effusion / Pericardial effusion
Air bronchogram or airway changes	Nodules including tree in bud opacities
Vascular enlargement	Mediastinal lymphadenopathy
Reticular pattern or linear opacities	Halo sign, Reverse Halo Sign or Atoll Sign
Pulmonary Thromboembolism	Air Bubble Sign
	Sub-pleural atelectasis
	Cavitation or cavity within a consolidation, mass or nodule.
	Bronchiectasis

Stages of Covid 19 pneumonia and Lung changes

In patients recovering from Covid-19 various stages of Lung involvement are defined on CT scans as shown in table 2. Initial lung findings are small sub pleural ground glass opacities which may be uni or bilateral with usually a lower lobe distribution that grow larger with Crazy paving and Consolidation.

Lung involvement progress to dense Consolidation up to two weeks from onset of initial symptoms. Subsequently the lesions are gradually absorbed leaving behind Ground glass opacities and Sub pleural bands. Most of the lesions resolve completely.

Table 2 – stages of Covid -19 pneumonia

Day of symptoms	Phase	Imaging findings
0-5 days Early stage1	exudative stage (leakage of fluid into interstitial)	Normal. Presence of unilateral/bilateral ground glass opacities predominantly in lower lobe, usually posteriorly distributed with the predilection for sub pleural and peripheral involvement
5-9 days Progressive Stage 2	Inflammatory stage (alveolar leak of protein/fluid resulting in diffuse alveolar opacities, increasing exudation-consolidation, progression to	Diffuse GGO / crazy paving , mixed GGO and consolidation pattern ,Multi lobar distribution
9-13 days Peak, stage 3	white out lungs- ARDS) Interstitial changes are due to septal congestion, edema, cellular infiltration, inflammation, hemorrhage and early fibrosis	Bilateral multilobe distribution Complex evolution into dense consolidation. Interstitial changes manifests as crazy paving, sub pleural bands/ linear opacities are seen in this phase
>14 days Absorption, Stage 4	Stage of resolution /Organizing pneumonia/ Post Covid fibrotic like changes	Gradual resorption of consolidation (Crazy paving no longer seen) Parenchymal bands / Atelectasis/ fibrosis in bilateral sub pleural lung fields Increased area of GGO involvement but density of GGO decreased (tinted sign/ melting sugar) GGO and fibrotic strips GGO completely resolved (in a median period of two weeks in many)
Upto 6 months	Delayed absorption / Post Covid fibrotic like changes	GGO and interstitial thickening Traction bronchiectasis, parenchymal bands, and/or honeycombing. Some may show complete resolution from scarring.
>6 months	Probable Post Covid fibrosis	Traction bronchiectasis, parenchymal bands, and/or honeycombing. Few areas of GGO/ reticulation may present.

The CORADS is basically a CT scan-based system that is used to assess the suspicion of pulmonary involvement in Covid 19.

Table 3 – CO-RADS category and CT findings

CORADS Category	level of suspicion for pulmonary involvement	CT findings	Summary
0	study not interpretable	Incomplete or of insufficient quality, because of severe artifacts due to coughing or breathing	study technically insufficient to assign a score
1	Very low	Very low level of suspicion for pulmonary involvement by COVID-19 based on either normal CT results or CT findings of unequivocal non-infectious origin. Mild or severe emphysema, perifissural nodules, lung tumors, and fibrosis	Normal or non-infectious
2	Low	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.Example bronchitis, infectious bronchiolitis, bronchopneumonia, lobar pneumonia, and pulmonary abscess with CT findings including tree-in-bud sign, a centrilobular nodular pattern, lobar or segmental consolidation, and lung cavitation	typical for other infection but not Covid -19
3	Indeterminate / Unsure	Pulmonary involvement of COVID-19 based on CT features that can also be found in other viral pneumonias or non-infectious 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, patterns of consolidation compatible with organizing pneumonia without other typical findings of COVID-19	Findings suggestive of Covid but also other diseases

4	High	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 include ground-glass opacities with or without consolidations 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	Suspicious for Covid-19
5	Very High	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, multifocal bilateral distribution, the vicinity to the minor or major fissure is also typical. Sub pleural sparing can be present. Crazy paving pattern, Sub pleural curvilinear bands or bands of ground glass with or without consolidation in a tethered arching pattern with small connections to the pleura are also considered typical findings. Thickened vessels within lung abnormalities are typical	Typical for Covid 19
6	Proven	Introduced to indicate proven COVID-19, as signified by positive RT-PCR test results for virus-specific nucleic acid	RTPCR positive for SARS-CoV-2

CT severity scoring A CT severity score is assigned to an individual study to decide upon the aggressiveness of the treatment. The system is a visual based scoring which assigns a score of 0-5 to each of the 5 lobes based on the extent of involvement (No involvement -0, <5%---1 between 6-25% involvement -----2, between 26-50%---3 between 51-75%----4 and over 75% ---5). The total scoring is out of 25. Scores between 1-8 are

considered mild, between 9-17 are considered of moderate disease severity and anything above 18 is considered severe. It is observed that severe score cases show a relatively poor outcome. Severe lymphopaenia, Increasing CRP levels, Serum Ferritin levels and D-Dimer levels are also observed with Increasing CT severity score as is the Oxygen Requirement and length of stay in the hospitals.

Table 4 -CT severity score

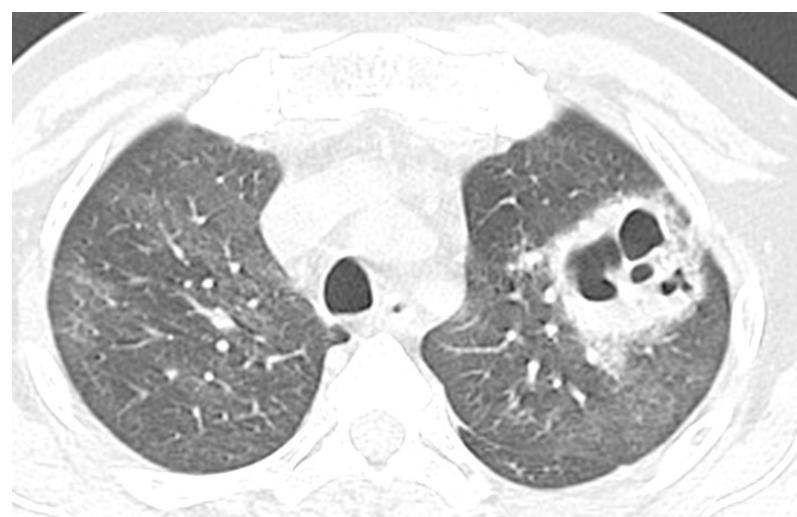
LUNG LOBES	CT Severity Score	Lung Lobe Involvement & Score
Right upper lobe		SCORE 0: 0% Involvement
Right middle lobe		SCORE 1: < 5% Involvement
Right lower lobe		SCORE 2: 5-25 % Involvement
Left upper lobe		SCORE 3: 25-50 % Involvement
Left lower lobe		SCORE 4: 50-75% Involvement
Total CT severity score (25)	/25	SCORE 5: >75 % Involvement
(score <8 –mild, 9-17 moderate, >18 severe)		

Table 5 – coinfection and secondary infections associated with Covid -19 pneumonia

COVID 19 PNEUMONIA - COINFECTIONS AND SECONDARY INFECTIONS- IMAGING FEATURES			
Gram negative bacteria	Corona virus Disease-Associated Mucormycosis (CAM).	influenza-associated pulmonary aspergillosis (IAPA)	COVID-19-associated pulmonary aspergillosis (CAPA)
Bilateral recent onset consolidation with or without necrosis	Mass like consolidation, crosses the fissures. Multiple nodular ground glass opacity /consolidation.	wedge-shaped lobar or segmental consolidation with air bronchogram, cavity formation, tree in bud pattern	May exhibit non-specific CT findings, such as bilateral areas of ground-glass opacity or crazy paving, extensive consolidations associated with peripheral traction bronchiectasis
Multiple cavitating nodules / abscess	Cavity- Birds nest formation / Reverse halo sign is seen.	nodules with halo signs	peribronchial consolidation
Unilateral pleural effusion	pleural effusion	bronchial wall thickening seen	bronchial wall thickening seen
	concomitant Sinusitis	tracheobronchitis with tracheal and bronchial ulceration	pseudo aneurysm
	voricanazole prophylaxis +		Serum galactomannan antigen test positive



(a)



(b)

Fig 5. Corona virus Disease-Associated Mucormycosis- left upper lobe cavitating consolidation as noted on sagittal (a) and axial (b) images; note the ground glass changes elsewhere, consistent with Covid infection.

Neurological manifestation of COVID -19 disease and imaging:

Covid -19 disease has now been recognized as a multisystem disease with increased recognition of neurological manifestations. The possible explanation for neurological involvement in Corona virus disease (COVID) can be grouped into four categories: 1) Direct effect due to neuro invasion by virus, 2) Para infectious immune response to infection manifesting as coagulopathy or cytokine storm. 3) Delayed immune response post infection.4) Complications of prolonged illness and hospitalization.

MRI is the imaging modality of choice and sequences should be tailored to the clinical indication. Sequences like SWI and post contrast FLAIR should be done in indicated cases. Patients presenting with acute stroke (hemorrhagic or ischemic): CT Brain with CTA brain and intracranial vessels or MRI Brain with MR angiogram can be performed. For Spinal manifestation MRI spine with contrast can be performed.

Neurological manifestations of COVID:

Neurological manifestations may vary from non-specific symptoms such as headache, dizziness, myalgia and/or fatigue, olfactory or taste dysfunction to specific syndromes including meningitis, stroke, and acute transverse myelitis and Guillain-Barre syndrome.

1. Thromboembolic infarcts: It's the most commonly seen intracranial manifestation and pathogenesis is due to development of coagulopathy or endothelial dysfunction. Acute stroke has strong prognostic indicator for poor outcome. Thromboembolic episodes may coincide with increased D-dimer levels and inflammatory markers. The commonly observed patterns of acute cerebral thromboembolic disease are large vessel occlusion with territorial infarcts, branch vessel occlusion, small vessel occlusion, small vessel infarcts, watershed infarcts, and

extensive bilateral multivessel infarcts (Fig 1). Diffuse central nervous system vasculitis pattern has also been encountered. Small vessel microangiopathy has been related to propensity of COVID- 19 to infect endothelial cells of different vascular beds. COVID 19 patients with thromboembolic complication have a higher clot burden with thrombus in other vessels like the cervical carotid, vertebral arteries, pulmonary arteries and lower extremity veins^{1,2}.

2. Hemorrhage: Patients with COVID 19 have hemorrhage in different location of the brain due to combination of factors like COVID 19 induced coagulopathy, disseminated intravascular coagulation & cytokine storm. Effects of treatment like thrombo prophylaxis, dialysis and ECMO are also contributory. Critical illness associated micro bleeds and virus induced thrombotic microangiopathy is responsible for micro hemorrhage which is seen distributed in the region of corpus callosum and at grey white matter interphase (Fig 2). Micro bleeds are suggested due to hypoxia-induced hydrostatic or chemical effects on the blood-brain barrier (BBB) potentially accounting for the extravasation of erythrocytes.
3. Leukoencephalopathy: Manifests as symmetrical confluent white matter T2 hyper intensity and diffusion restriction sparing the juxtacortical and infratentorial white matter (Fig 3). These findings are non-specific or related to delayed post hypoxic phenomenon.
4. Global hypoxic injury: Global hypoxic injury has been reported with predominately involvement of the basal ganglia, thalamus, hippocampi and cortex (Fig 4). Unusual pattern of isolated involvement of the Globus pallidi has also been seen. Other pattern seen is delayed post hypoxic leukoencephalopathy.

5. **Other manifestations include:**
- a. Posterior reversible encephalopathy syndrome (PRES): Vasogenic or cytotoxic edema distributed in the watershed territory of the cerebral hemisphere with predominant parieto-occipital lobe predilection. They may also present with hemorrhage or micro bleeds.
 - b. Meningitis and encephalitis: Meningitis and encephalitis are uncommon in COVID patient. The MRI features include multifocal involvement of the brain most characteristically in the thalamus, brain stem, cerebral white matter, and cerebellum. ADEM and acute hemorrhagic leukoencephalopathy has also been described. The changes may be related to intracranial cytokine storm and BBB breakdown.
 - c. Cytotoxic lesion of the corpus callosum: It has been described both in adults and children with COVID 19. These lesions are due to inflammatory damage from coincident cytokine storm.
 - d. Olfactory bulb involvement: Edema in the olfactory bulb and track with increased T2 signal intensity in the gyrus rectus. Olfactory bulb atrophy after COVID 19 induced anosmia has also been described.
 - e. Cranial nerve enhancement: Cranial neuropathies reported in COVID 19 include optic neuritis, oculomotor nerve enhancement and Miller Fisher syndrome. On imaging there is mild thickening and enhancement of the oculomotor nerve.
 - f. Spinal manifestation: Guillain Barre syndrome is seen in association with COVID 19 characterized by T2 hyper intensity in the distal cord and enhancement of the caudal nerve roots.

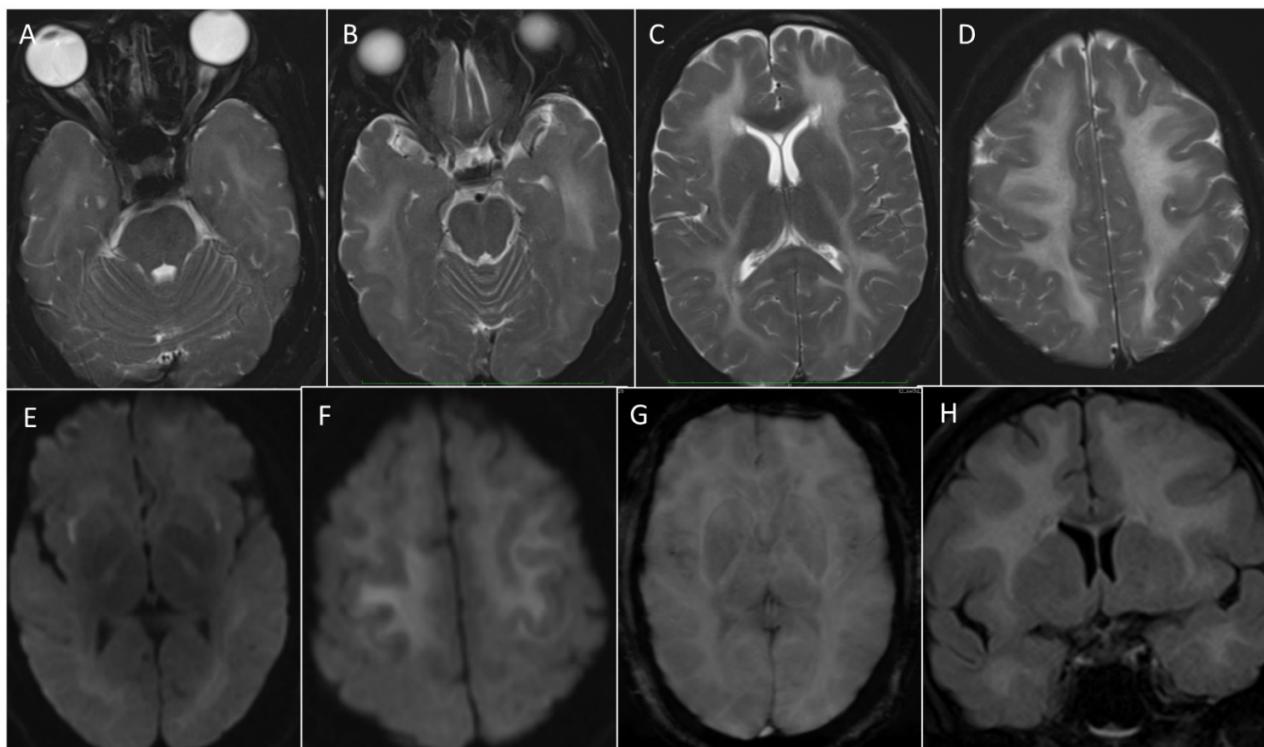


Figure 6. Leukoencephalopathy. 41-year-old male with history of COVID 19 infection presented with seizures progressing to altered sensorium. MRI of the brain Axial T2 (A - D), Axial DWI (E & F), Axial GRE (G) and Coronal T1(H) revealed confluent white matter hyperintensity involving bilateral cerebral hemispheres with corresponding areas of diffusion hyperintensity. No hemorrhage or abnormal mineralization noted.

(Figure 7 to 13 on Color pages section)

Table 6- Imaging findings in acute invasive fungal rhino sinusitis

IMAGING IN ACUTE INVASIVE FUNGAL RHINO SINUSITIS / MUCORMYCOSIS		
SINO NASAL AND NECK SPACES	ORBIT	INTRACRANIAL
<ul style="list-style-type: none"> Nasal cavity o Emphysematous /ulcerated mucosal thickening- especially unilateral o Nasal septum ulceration/abscess o Necrotic turbinate/ black turbinate sign / lack of enhancement. 	<ul style="list-style-type: none"> • Bony orbit • Preseptal edema • Extraconal fat involvement, sub periosteal abscess • Orbital muscle cone involvement, proptosis • Intraconal fat involvement • Sub periosteal collection • Orbital apex involvement, superior and inferior orbital fissure • Globe involvement • Optic nerve involvement. • Superior ophthalmic vein thrombosis 	<ul style="list-style-type: none"> o Skull base involvement –clivus, frontal, ethmoid, sphenoid and basi occiput o Skull base foramen & Perineural extension, pterygoid plates o Meningitis o Cortical edema – focal cerebritis. (frontal, anteromedial temporal lobe) o Intracranial granulomas/ abscess o Extra-axial/ parenchymal collection o Infarct/hemorrhage o Cranial nerve / Meckel's cave involvement. <p>Vascular complications</p> <ul style="list-style-type: none"> o Cavernous sinus thrombosis o Internal carotid artery narrowing/ thrombosis/ pseudo aneurysm

- g. Mucormycosis: Amidst the pandemic of COVID 19 there has been a surge of rhino cerebral Mucormycosis. The CNS involvement is via contiguous extension through the cribriform plate or following skull base involvement and perineural spread. Imaging manifestations include skull base osteomyelitis, pachymeningeal enhancement, leptomeningeal enhancement, and cerebritis progressing to abscess, cranial nerve infiltration, infarcts, cavernous sinus thrombosis, mycotic pseudoaneurysm, subarachnoid hemorrhage and intraparenchymal hemorrhage.

HEAD AND NECK MANIFESTATION OF COVID -19 DISEASE AND IMAGING OF ACUTE INVASIVE FUNGAL RHINOSINUSITIS

Acute invasive fungal rhino sinusitis (AIFRS) is a result of weakened host immune system and a rapidly progressive disease. Rapid rise has been seen in incidence of AIFRS in association with COVID 19 especially in the setting of concomitant diabetes mellitus and steroid administration.

The disease carries a high mortality with a large meta-analysis showing mortality rate of 50%. Most disease in the current situation is caused by Mucormycosis but aspergillus and other bacterial infections can also show similar changes. A high index of suspicion with knowledge of various clinical and imaging red flag signs helps in early diagnosis, early initiation of treatment and aids to reduce morbidity and mortality from the disease.

Imaging modalities include Contrast enhanced CT scan of PNS and nasal cavity and MR examination of PNS and nasal cavity with contrast.

Table 7 - abdominal, peripheral vascular and cardiac manifestations of corona virus disease - radiological imaging findings.

Abdominal manifestations:

1. Bowel wall thickening (small and large bowel) in 15-31% associated with hyperemia and mesenteric thickening.
 2. Fluid-filled colon (homogeneous fluid attenuation contents in the lumen of colon without formed stool) without wall thickening or pericolonic stranding.
 3. Mesenteric ischemia (Enteritis accompanied by ischemia)
 4. Pneumatosis intestinalis or portal venous gas in approximately 10%
 5. Acute Pancreatitis
 6. Solid organ infarctions or vascular thromboses (18%)
 7. Mesenteric stranding
 8. Ascites
 9. Gallbladder sludge, newly found hepatosteatosis, hepatitis, acute liver injury
 10. Enlarged kidneys, bilateral renal infarcts and other abnormalities of the urinary tract (12%): cystitis, pyelonephritis, renal abscess
 11. Ileocolic intussusception (in pediatric population)
 12. Nonspecific: Gastritis, equivocal findings of appendicitis, perforated marginal ulcer at the gastro-jejunal anastomosis in a gastric bypass patient, stercoral colitis, and concurrent stercoral colitis and diverticulitis, liver abscess, progression of hepatic metastases
-

Peripheral vascular manifestations

- Venous thromboembolism - DVT- Lower and upper extremity Doppler US is the first-line imaging modality for diagnosis of peripheral venous thrombosis and can be performed at the bedside. On compressible veins, echogenic clot and minimal or absent flow within a distended vein are the US hallmarks of acute or subacute DVT
- Superficial thrombophlebitis - manifested by hyperemia of thrombotic vessel wall on colour Doppler USG.
- Arterial thrombosis -Doppler US and CT angiography of the extremity vessels are both instrumental in the evaluation of peripheral arterial thrombosis. At US, absence of flow within an arterial segment is diagnostic of an occlusive thrombus.

Cardiac manifestation

- Myocarditis
- Pericarditis
- Acute coronary syndrome
- Thromboembolic events

Multisystem inflammatory disorder:

MIS-C is a newly described syndrome associated with COVID-19. Unlike typical COVID-19, which presents primarily with respiratory symptoms and pneumonia, MIS-C associated with COVID-19 typically presents with multiorgan injury, predominantly involving the cardiovascular system. Pulmonary manifestations are distinctly uncommon. In the abdomen, the most common imaging findings are ascites, hepatomegaly, and echogenic kidneys, reflecting an underlying multiorgan inflammatory process. Given the nonspecific clinical presentation of MIS-C associated with COVID-19, imaging evaluation plays an important role in making the diagnosis. Radiologists should be aware of the constellation of these imaging findings that, although

nonspecific, when combined with the clinical presentation and a history of exposure to SARS-CoV-2, should suggest the diagnosis of MIS-C associated with COVID-19, because patients may rapidly deteriorate. Although most patients with MIS-C who are admitted to the hospital are severely ill and require admission to the PICU, most improve clinically with appropriate management after accurate diagnosis. Nevertheless, the long-term outcome of MIS-C is yet to be determined. Most common thoracic imaging findings were cardiomegaly, congestive heart failure or cardiogenic pulmonary edema, and pleural effusions. Pneumonia, although reported with high incidence in pediatric and adult patients with COVID-19, is uncommon in MIS-C associated with COVID-19. Abdominal imaging findings were notable for ascites, hepatomegaly, and echogenic kidneys in approximately one-third of the patients and for other findings in several patients, including thickened gallbladder, bowel, and urinary bladder walls and bowel distention, reflecting an underlying multisystemic inflammatory process. MIS-C is a syndrome of multisystemic inflammation in which patients present with a high sustained fever and gastrointestinal and mucocutaneous symptoms with rapid progression to cardiogenic shock and multisystem injury. Although the abdominal imaging findings of MIS-C are nonspecific, they mirrored the clinical and laboratory findings. Hepatic injury based on blood chemistry results was present in the majority of patients, and one-third of patients developed acute kidney injury. Imaging findings of hepatomegaly and echogenic kidneys reflected parenchymal injury to these organs in approximately one-third of the patients. Ascites and bowel, gallbladder, and urinary bladder wall thickening were also identified and may have reflected inflammation or low serum albumin levels.

Other system involved in covid -19 disease are gastrointestinal system, hepatobiliary, peripheral vascular and cardiovascular system(table -7)

COVID -19 DISEASE IN SPECIAL CONDITIONS:

1. Covid -19 and pregnancy: It is hypothesized that, owing to alterations in physiology associated with Pregnancy, these patients may have an increased risk of infections in general. Pregnancy and delivery did not aggravate the severity of COVID-19 pneumonia CT in pregnant patients, it is preferable to use a low-radiation-dose imaging mode to decrease the risk of maternal and fetal radiation exposure, and whenever possible the abdomen and pelvis should be covered by a lead blanket.
2. Covid 19 and oncology: Covid -19 have a higher case fatality in cancer patients than the individuals without cancer. Certain imaging features seen in Covid 19 patient may overlap with cancer imaging features.

Conclusion:

The clinical presentation, course, and outcome of COVID-19 are heterogeneous. It primarily affects the respiratory system but has also been shown to impact other systems in the human body, resulting in multiorgan injury and, in some cases, failure. Imaging plays a significant role in the detection, diagnosis, and assessment of virus-induced injury and associated complications. Low-radiation-dose chest CT is recommended unless CT pulmonary angiography is required to evaluate for PE. Several chest CT features are commonly seen in COVID-19 (including ground-glass opacities, vascular enlargement, bilateral abnormalities, lower lobe involvement, and posterior predilection), whereas others are not, and this may help in diagnostic decision making. The appearance of COVID-19 on chest CT images follows a somewhat predictable pattern over time. Notably, asymptomatic patients with SARS-CoV-

2 infection frequently have normal chest CT examination results, and the proportion of symptomatic patients with COVID-19 and a normal chest CT examination is non negligible. Furthermore, lung abnormalities on chest CT images are nonspecific for COVID-19. CT appearance of 2019-nCoV shares some similarities with that of other diseases that cause viral pneumonia, particularly those within the same viral family (SARS and MERS). Rhino cerebral Mucormycosis and neurological complication of Covid 19 disease will increase the patient mortality if not recognized at correct time. A thorough knowledge of diagnostic imaging hallmarks, atypical imaging features, multisystem manifestations, and evolution of imaging findings is essential to optimize patient care.

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Review on Complications of COVID 19



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COVID-19 is a new rapidly spreading epidemic. The symptoms of this disease could be diverse as the virus can affect any organ in the body of an infected person. While most people with COVID-19 recover and return to normal health, some people can have symptoms that last for weeks or even months after recovery from acute illness. People are not infectious to others during this time. This persistent state of ill health is known as 'post COVID condition' but other names are also used to describe the condition. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms. Some patients develop medical complications that may have lasting health effects. The main objective in this review to give an overview of COVID 19 complications (Highly Likelihood) then overview about less likelihood complications.

1. Post Intensive care syndrome

COVID-19 patients treated in the in the ICU can present with post intensive care syndrome, a range of cognitive, psychiatric, & physical disability (e.g., muscle weakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium) that disturbs survivors of critical illness, and continues after the patient has been discharged from the ICU. Weakness affects 33% of patients who receive mechanical ventilation, 50% of patients with sepsis (> 1 week in ICU). The risk can be minimized with medication management, physical rehabilitation, family support, and follow-up clinics.¹

2. Venous thromboembolism

The pooled incidence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism in hospitalized patients was 14.7, 11.2%, and 7.8%, respectively. The prevalence was significantly higher in patients admitted to the in ICUs, despite thromboprophylaxis. COVID-19 patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism. Patients may be predisposed to venous thromboembolism due to the direct effects of COVID-19, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors). Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity. Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring. If venous thromboembolism is suspected, perform a CT angiography or ultrasound of the venous system of the lower extremities. Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalized patients. Direct oral anticoagulants are the preferred option in outpatients provided there is no potential for drug-drug interactions. Anticoagulation therapy is recommended for a minimum of 3 months.^{1,2}

3. Cardiovascular complications

- a) **Myocardial injury and myocarditis-** studies have found that myocardial injury with an elevated troponin level may occur in 7–17% of patients hospitalized with COVID-19 and 22–31% of those admitted to the intensive care unit (ICU). In fact, one study suggested that up to 7% of COVID-19 related deaths were due to myocarditis. In patients with myocarditis and myocardial injury, serum troponin values will be abnormal. The ECG abnormalities result from myocardial inflammation and include non-specific ST segment-T wave abnormalities, T wave inversion, and PR segment and ST segment deviations (depression and elevation). Moreover, troponin elevations in patients with COVID-19 infection have been directly associated with an increased risk of adverse outcome in those patients with severe infection, including mortality.

b) Acute myocardial infarction

Severe systemic inflammation increases the risk of atherosclerotic plaque disruption and AMI . Due to extensive inflammation and hypercoagulability, the risk of AMI is likely present in patients with COVID-19. Patients who are hemodynamically unstable in the setting of NSTEMI should be managed similarly to those with STEMI

c) Acute heart failure and cardiomyopathy

Acute heart failure can be the primary presenting manifestation of COVID-19 infection. & present in 23% of patients in their initial presentation for COVID-19, with cardiomyopathy occurring in 33% of patients it is important to be conscious of this potential cardiac dysfunction when administering intravenous fluids and avoid overaggressive fluid replacement.

d) Dysrhythmias

Palpitations may be a presenting symptom in over 7% of patients with COVID-19. A range of dysrhythmias have been encountered in patients with COVID-19 infection. Most frequently, sinus tachycardia is seen in such patients, resulting from multiple, simultaneous causes (hypoperfusion, fever, hypoxia, anxiety, etc)³

4. Respiratory Complications of Covid

- a) **Acute respiratory failure** Reported in 8% of patients in case series. Leading cause of mortality in patients with COVID-19. Children can quickly progress to respiratory failure. Patients with COVID-19 may have a higher risk of developing ventilator-associated pneumonia compared with patients without COVID-19.¹

- b) Long term respiratory complications of covid-19 patients recovering from covid-19 and identifies potential respiratory problems including chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease. The evidence for these possible sequelae is largely derived from acute manifestations of covid-19.^{1,4}

5. Cytokine release syndrome

Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death. Elevated serum pro-inflammatory cytokines (e.g., TNF alpha, IL-2, IL-6, IL-8, IL-10, granulocyte- colony stimulating factor, monocyte chemoattractant protein 1) and inflammatory markers (e.g., C- reactive protein, serum ferritin) have been commonly reported in patients with severe COVID-19. Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.

However, the pooled mean serum interleukin-6 level was markedly less in patients with severe or critical COVID-19 compared with patients with other disorders associated with elevated cytokines such as cytokine release syndrome, sepsis, and non-COVID-19-related ARDS. These findings question the role of cytokine storm in COVID-19-induced organ dysfunction, and further research is required.¹

6. Acute kidney injury

Acute kidney injury is common amongst patients with SARS-CoV-2 infection, especially critically ill ones, and is without a doubt associated with higher mortality. There are numerous possible pathomechanisms which are still being investigated, but the most probable ones are direct cellular invasion, ARDS, cytokine storm and hypovolemia. Histopathological reports showed that most COVID-19 patients with AKI presented acute tubular damage, sometimes with necrosis and collapsing glomerulopathy. The most important steps that should be taken in AKI prevention are the following: minimizing the risk of hypovolemia and monitoring serum creatinine levels in the early stages of COVID-19 infection, especially in regard to the high-risk patients at an older age with diabetes mellitus, hypertension and cardiovascular diseases. Furthermore, physicians must be aware that patients who recover from AKI induced by SARS-CoV-2 require monitoring of their kidneys on follow-up, as there is rising evidence showing eGFR decreases among patients with a history of COVID-19-associated AKI.⁵

7. Acute liver injury

Deranged liver enzymes are not an uncommon finding in COVID-19 patients. Usually, it is in the form of altered

aminotransferases picked up during routine investigations. Seldom does it present with acute hepatitis. The cause of the liver injury is not clearly established, but most likely, it seems multifactorial, with a cytokine storm and immune dysregulation possibly playing a role so it could be hypoxia, hypotension, multiple drugs, direct viral effect, and ICU-related infections. In the majority of patients, the liver injury seems to be self-limiting, not requiring any specific intervention, and not associated with acute liver failure.⁶

8. Neurological complications

Significant neurologic complications are associated with COVID-19, such as impaired level of consciousness, cerebrovascular disease, encephalitis, encephalopathy, and GBS. Some of the medications utilized to treat COVID-19 also have potential neurologic effects and may interact with medications of pre-existing neurologic disease. Emergency medicine clinicians must be cognizant of these neurologic complications when treating COVID-19.

Acute cerebrovascular disease remains one of the more common and serious neurologic complications seen in COVID-19 populations. Interestingly, COVID-19 has also led to younger patients presenting with ischemic stroke, including large vessel occlusions. Additionally, COVID-19 patients can develop significant hypoxia leading to decreased cerebral oxygenation and infarcts, particularly in those with pre-existing cerebrovascular disease. Infection, inflammation, and hypercoagulable states can further increase the risk of ischemic stroke, which can be even more pronounced in older patients.⁷

9. Post-COVID-19 syndrome (long COVID)

Also known as post-acute COVID-19, post-acute COVID-19 syndrome, chronic COVID,

long-haul COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), and post-COVID conditions.

Definition : signs and symptoms that develop during or after an infection consistent with COVID- 19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Ongoing symptomatic COVID-19 is defined as signs and symptoms from 4 weeks up to 12 weeks. The syndrome is not thought to be linked to disease severity or specific signs and symptoms during the acute phase of illness. There is no standardized case definition and case definitions vary. For example, the US Centers for Disease Control and Prevention defines post-COVID conditions as an umbrella term for the wide range of health consequences that are present more than 4 weeks after infection with SARS-CoV-2.

Epidemiology : frequency ranges from 4.7% to 80% across observational studies, and occurs between 3 to 24 weeks after the acute phase or hospital discharge. Potential risk factors include older age, age 40 to 49 years, female sex, obesity, severe clinical status, higher number of comorbidities, higher symptom load, hospital admission, and oxygen supplementation in the acute phase, although data is lacking.

Diagnosis : use a holistic, person-centred approach that includes a comprehensive clinical history (including history of suspected or confirmed acute COVID-19, nature and severity of previous and current symptoms, timing and duration of symptoms since the start of acute illness, and a history of other health conditions), and appropriate examination that involves assessing physical, cognitive, psychological, and psychiatric symptoms, as well as functional abilities. Refer patients with signs or symptoms that could be caused by an acute or life threatening complication (e.g., severe

hypoxaemia, signs of severe lung disease, cardiac chest pain, multisystem inflammatory syndrome in children) urgently to the relevant acute services.

Signs and symptoms: symptoms vary widely, may relapse and remit or fluctuate, can change unpredictably, and can occur in those with mild disease only. Common long-term symptoms include persistent cough, low-grade fever, breathlessness, fatigue, pain, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, earache, tinnitus, sore throat, loss of taste/ smell, impaired mobility, numbness in extremities, dizziness, tremors, memory loss, mood changes, skin rashes, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions (e.g., anxiety, depression). Gastrointestinal sequelae including loss of appetite, nausea, acid reflux, and diarrhoea are common in patients 3 months after discharge. Some of the symptoms may overlap with post-intensive care syndrome (see above). The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.

Investigations: tailor investigations to the clinical presentation, and to rule out any acute or life-threatening complications and alternative diagnoses. Investigations may include blood tests (e.g., full blood count, kidney and liver function tests, C-reactive protein, ferritin, thyroid function), oxygen saturation, blood pressure and heart rate measurements, exercise tolerance test, chest imaging, electrocardiogram, and psychiatric assessment

Management : give advice and information on self-management including ways to self-manage symptoms (e.g., set realistic goals, antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged

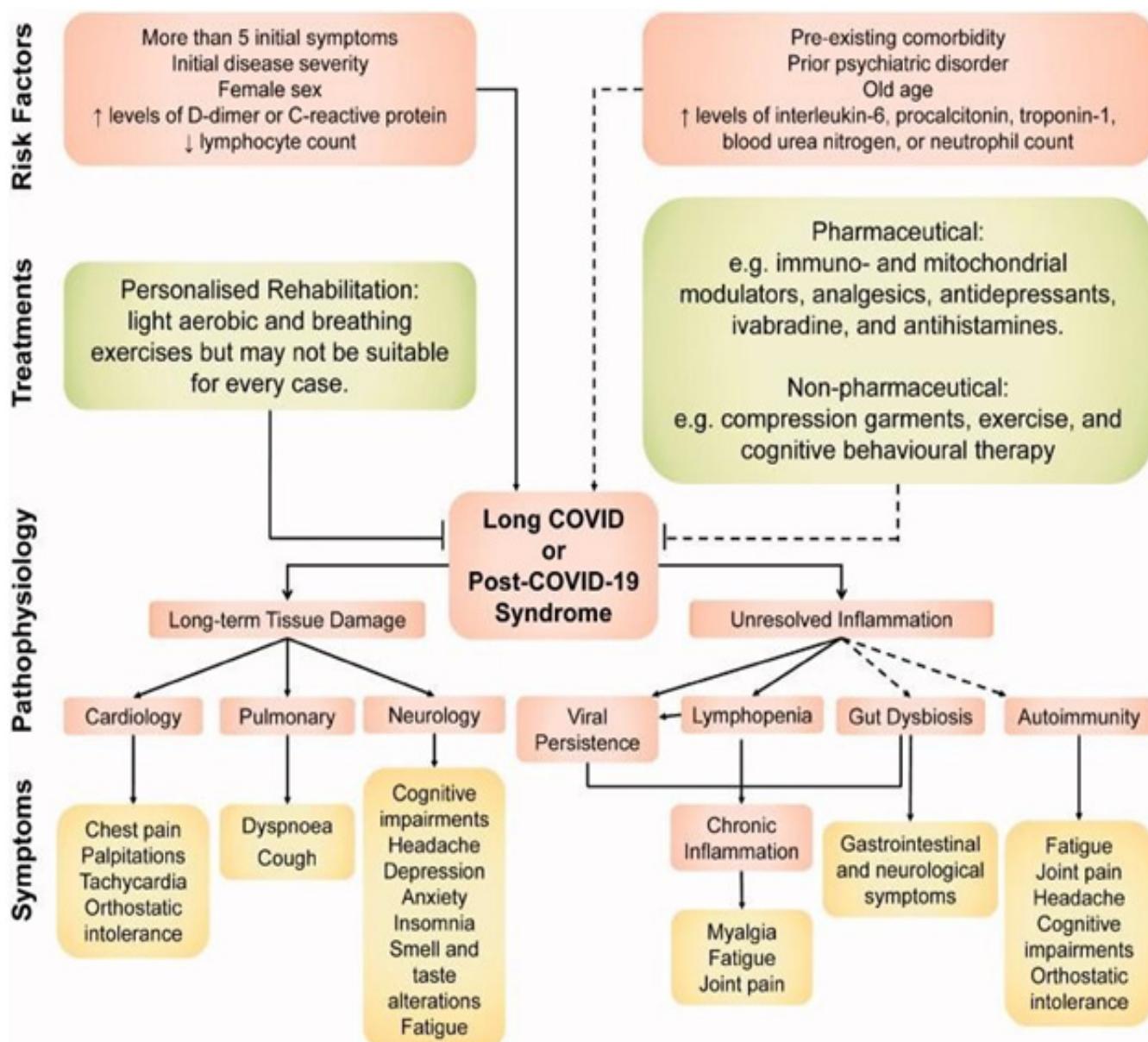


Fig 1-An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines

return to exercise); who to contact if there is concern about symptoms or if there is need for support; sources of support (e.g., support groups, online forums); and how to get support from other services (e.g., social care, housing, financial support).

A personalized, multidisciplinary rehabilitation plan that covers physical, psychological, and psychiatric aspects of rehabilitation is an important part of management. Many patients

recover spontaneously with holistic support, rest, symptomatic treatment, and a gradual increase in activity.

Referral to a specialist may be required in patients where there is clinical concern along with respiratory, cardiac, or neurological symptoms that are new, persistent, or progressive. Follow-up : agree with the patient how often follow-up and monitoring are needed (either in person or remotely), and which healthcare professionals

should be involved. Take into account the patient's level of need and the services involved. Tailor monitoring to the patient's symptoms, and consider supported self-monitoring at home (e.g., heart rate, blood pressure, pulse oximetry). Be alert to symptoms that could require referral or investigation.^{1,8,9}

10. Cutaneous & ocular complications of Covid

Patients with COVID-19 most commonly present with respiratory symptoms, but multiorgan involvement can occur, with multiple skin manifestations. Dermatologic findings may include a maculopapular rash, urticaria, vesicular rash, petechia, purpura, chilblains, livedo racemosa, and distal ischemia. These rashes should trigger consideration of COVID-19, and understanding these manifestations is important to help identify potential COVID-19 patients and properly treat complications.¹⁰

The most common ocular symptoms include dry eye or foreign body sensation, redness, tearing, itching, eye pain, and discharge (8.8%). Conjunctivitis was the most common ocular disease in patients with ocular manifestations (88.8%). Retinal complications that may lead to vision loss have also been reported.

Sequelae and complications from demyelinating disease and stroke require management in conjunction with other specialties such as neurology, occupational therapy, and physical medicine and rehabilitation. Ophthalmologists need to be vigilant as we continue to learn of the different ways that COVID-19 may affect the eye and periorbital tissues.¹¹

11. Other complications

Other complications which include cardiac arrest, sepsis/septic shock, disseminated intravascular coagulation, vaccine-induced immune thrombocytopenia and thrombosis (VITT), mucormycosis, aspergillosis, autoimmune haemolytic anaemia, pancreatic injury, immune thrombocytopenia, subacute thyroiditis which are low likelihood and variable timeframes.¹

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Treatment Guidelines for Mild Disease and Home Isolation in Covid – 19



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Definition of Mild Disease:¹

Patients with COVID-19 infection can get a range of clinical manifestations, from no symptoms to critical illness. Patients who have any of the various signs and symptoms of COVID-19 (e.g., fever, sore throat, malaise, headache, cough, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging should be considered to have mild disease.

Features of mild disease are enumerated as below:

- No shortness of breath/difficulty in breathing
- Respiratory rate < 24/min
- SpO₂: > 94% on room air
- Take 6 min walk test

Investigations:

Anyone with symptoms consistent with COVID-19, should be tested for COVID-19 infection. RT-PCR based test or an antigen test should be used to detect COVID-19 virus.

RT-PCR Based Testing for COVID-19 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests are considered the gold standard for detecting COVID-19 infection. These tests detect the nucleic acids of COVID-19 virus. There may be a window period of up to 5 days after exposure before viral nucleic acids can be detected in nasal/oral swabs. RT-PCR based tests may produce false negative results if a mutation occurs in the part of the genome of the virus that is assessed by that test.² False negative results are more likely to occur when using RT-PCR that rely on only one target. Therefore, a single negative test result does not exclude the possibility of COVID-19

infection in people who have a high likelihood of infection based on their exposure history and their clinical presentation.³ Most of the commercial RT-PCR based tests rely on multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.⁴ RT-PCR tests that use multiple targets are less likely to be impacted by an increased prevalence of genetic variants.

Rapid Antigen Test [RAT]

Antigen based diagnostic tests which detect viral antigens, are less sensitive than RT-PCR-based tests, but they have similarly high specificity. Antigen tests are performed best early in the course of symptomatic COVID-19 infection, when the viral load is highest. Advantages of antigen-based tests are their low cost and rapid turnaround time. The immediate results makes them an attractive option for point-of-care testing. Additional RT-PCR based test is recommended when a person who is strongly suspected of having COVID-19 infection gets a negative result, and when a person who is asymptomatic gets a positive result.⁵

Serologic or Antibody Testing

Antibody tests are not used for Diagnosis of COVID-19 Infection. RT-PCR and antigen tests for COVID-19 detect the presence of the COVID-19 virus but serologic or antibody tests detect recent or prior COVID-19 infection. It may take 21 days or longer after symptom onset for seroconversion to occur so these tests cannot be used for symptomatic patients for confirmation of the disease.⁶⁻⁷

Other Investigations

No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with

underlying comorbidities are at higher risk of disease progression therefore, health care providers should monitor these patients closely until clinical recovery is achieved.

Treatment :

Patients with suspected or laboratory-confirmed COVID-19 should be ideally have teleconsultation before they come to hospital. Most mildly ill patients can be managed at home through teleconsultations. We can use patient self-assessment tools for this. The management plan should depend on vital signs, oxygen levels, risk factors for progression to severe disease and the availability of health care resources.

If it is decided to continue treatment at home, proper guidelines should be given for the patient and caregiver. We should ensure that a caregiver is available 24X7 and should have access to health care centre in case the emergency arises.

General Guidelines for the patient

The first and most important point is that the patient should live in a separate room. The room should be ventilated so that fresh air keeps coming through but care should be taken that others are also safe and the air from his room should not go to the areas where others are exposed.

There should be one identified person who is the caregiver and that he should have no underlying high risk condition. Whenever caregiver goes to the patients room, patient as well as caregiver should wear mask, preferably N95. Distance of more than 2 meters should be maintained and duration of the stay in the room should be as less as possible. As soon as the caregiver leaves the room, he should dispose off the mask and wash his hands. He should avoid touching the face, nose or mouth before washing the hands.

Table 1: Self-monitoring tool

Day of symptoms and time (every 4 hourly)	Temp	Heart rate (from pulse oximeter)	SpO2 % (from pulse oximeter)	Feeling (better /same /worse)	Breathing (better /same /worse)

Also, the patients should have their own dishes and cups, towels and bed linens. And these can be washed with soap and water at least once a day. Also surfaces touched by the patient frequently have to be cleaned and disinfected every day and any waste generated from that patient should be packed and disposed safely.

Patient should have healthy balanced diet in form of fruits and vegetables with proper hydration. Patients and family should stay connected and engage in positive talks through phone, video-calls, etc. He should engage in recreational activities such as book reading, drawing, painting etc to keep himself occupied.

Patients with dyspnea may benefit from resting in the prone position rather than the supine position.⁸ They should also do breathing exercises⁹ in form of yoga or incentive spirometry. Proper adequate rest is recommended as needed during the acute phase of the disease and ambulation and other forms of activity should be increased according to the patient's tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery

Self-monitoring for fever, breathlessness, SpO2 or worsening of any symptoms should be done regularly. An example of such a monitoring tool is given below. (Table 1)

Patient should be in communication with a treating physician and should report any deterioration at the earliest.

Medications

Symptomatic treatment includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough.

Inhalational Budesonide (given via Metered dose inhaler/ Dry powder inhaler) at a dose of 800 mcg BD for 5 days) to be given if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.

Anti-COVID-19 Monoclonal Antibodies

Two combination anti-COVID-19 monoclonal antibody products (casirivimab plus imdevimab and bamlanivimab plus etesevimab) and a single monoclonal antibody (sotrovimab) have shown to reduce the risk of hospitalization and death in those with mild to moderate COVID-19 symptoms and certain risk factors for disease progression. These products have received Emergency Use Authorizations from various authorities for the treatment of COVID-19 in these individuals, as well as in those with other risk factors for progression that have been identified in studies. There are no comparative data to determine whether there are differences in clinical efficacy or safety between these products. At present these antibodies are recommended to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression. Treatment should be started as soon as possible after the patient receives a positive result on a COVID-19 antigen test RT-PCR based test and within 10 days of symptom onset. Casirivimab and imdevimab is easily available in India. It can be used in subcutaneous form also, whenever IV infusion is not possible. The subcutaneous injections should be given at 4 different sites in divided doses.

The conditions which were considered high risk in the studies for evaluation of efficacy of monoclonal antibodies in COVID-19 were:

- Age >65 years
- Obesity (BMI >30)
- Diabetes
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- An immunocompromising condition or

immunosuppressive treatment

- Chronic kidney disease
- Pregnancy
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19)

Medications which are used for treatment of COVID-19 but got out of favour after few trials :

Hydroxychloroquine or chloroquine

Chloroquine is an antimalarial drug that is in use for very long time and Hydroxychloroquine is an analogue. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Both chloroquine and hydroxychloroquine increase the endosomal pH, which inhibits fusion between COVID-19 and the host cell membrane.¹⁰ Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 (ACE2) receptor, which may interfere with the binding of COVID-19 virus to the cell receptor.¹¹ In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of COVID-19 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.¹² Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesized to be another potential mechanism of action for the treatment of COVID-19. The safety and efficacy of chloroquine or have been evaluated in randomized clinical trials, observational studies, and single-arm studies.

Nonhospitalized Patients Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with early, asymptomatic, or mild COVID-19.^{13,14} In an open-label trial, Mitja et al. randomized 307 nonhospitalized people who were recently confirmed to have COVID-19 to receive hydroxychloroquine or no antiviral treatment. Patients in the hydroxychloroquine arm received

hydroxychloroquine 800 mg on Day 1 followed by 400 mg daily for an additional 6 days. This study reported no difference in the mean reduction in COVID-19 RNA at Day 3 or the time to clinical improvement between the two arms.

Adverse Effects: Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine. Cardiac adverse events that have been reported in people who received hydroxychloroquine include QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths.¹⁵

Azithromycin

An open-label, prospective, randomized trial compared oral azithromycin 500 mg once daily for 3 days plus standard of care to standard of care alone in nonhospitalized, high-risk, older adults who had laboratory-confirmed or suspected COVID-19. No differences were observed between the arms in the primary endpoints of time to first self-reported recovery and hospitalization or death due to COVID-19. These findings remained consistent in an analysis that was restricted to participants with positive COVID-19 RT-PCR report. The study was ultimately halted due to futility.¹⁶ Similarly, in a preliminary report from ATOMIC-2, adding oral azithromycin 500 mg once daily to standard of care for 14 days did not reduce the risk of hospitalization or death among 292 participants with mild to moderate COVID-19.¹⁷

Azithromycin has antiviral and anti-inflammatory properties. When used in combination with hydroxychloroquine, it has been shown to have a synergistic effect on COVID-19 *in vitro* and in molecular modeling studies.^{18,19} However, despite demonstrating antiviral activity in some *in vitro* systems hydroxychloroquine plus azithromycin didn't reduce upper or lower respiratory tract viral loads or demonstrated clinical efficacy in a rhesus macaque model.²⁰

In another trial, treating patients who had asymptomatic or mild COVID-19 with hydroxychloroquine with azithromycin did not result in greater rates of virologic clearance (as measured

by a negative polymerase chain reaction [PCR] result on Day 6).²¹

The use of azithromycin has also been associated with QTc prolongation²² and using it in combination with hydroxychloroquine has been associated with a higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19.^{23,24}

Ivermectin

High concentrations of ivermectin have been shown to inhibit COVID-19 replication *in vitro*.^{25,26} Population data also indicate that country-wide mass use of prophylactic ivermectin, is associated with a lower incidence of COVID-19.²⁷ At this time, few clinical trials have evaluated the safety and efficacy of ivermectin for COVID-19 PrEP or PEP. Although several studies had reported potentially promising results, the findings were limited by the design of the studies, their small sample sizes, and the lack of details regarding the safety and efficacy of ivermectin.

In a descriptive, uncontrolled interventional study of 33 contacts of patients with laboratory-confirmed COVID-19, no cases of COVID-19 infection were identified within 21 days of initiating ivermectin for PEP.²⁸ An open-label randomized controlled trial investigated ivermectin prophylaxis (plus personal protective measures [PPMs]) in health care workers (as PrEP) or in household contacts (as PEP) exposed to patients with laboratory-confirmed COVID-19. The incidence of COVID-19 infection was lower among the participants who received ivermectin than among control participants who used only PPMs. However, the study provided no data on the characteristics of the study participants, types of exposures, or how endpoints were defined.²⁹ Finally, in a small case-control study in COVID-19-exposed health care workers, 186 participants who became infected were matched with 186 uninfected controls. Of those who received ivermectin after exposure to COVID-19, 38 were in the infected group and 77 were in the uninfected group, which led the investigators to conclude that ivermectin reduced the incidence of COVID-19 infection.³⁰ Several clinical trials that are evaluating the use of ivermectin for COVID-19 PrEP or PEP are currently underway

or in development. We can consider Tab Ivermectin (200 mcg/kg once a day, to be taken empty stomach) for 3 to 5 days.

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has antiinflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines.³¹ Because humans may require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because COVID-19 infection may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied. There is insufficient evidence to recommend either for or against the use of vitamin C for the treatment of COVID-19 in noncritically ill patients because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation.

Clinical Data on Vitamin C in Outpatients With COVID-19 Oral Ascorbic Acid Versus Zinc Gluconate Versus Both Agents Versus Standard of Care In an open-label clinical trial that was conducted at two sites. The patients were randomized to receive either 10 days of oral ascorbic acid 8,000 mg, zinc gluconate 50 mg, both agents, or standard of care.³² The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled ($n = 214$). Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events. The

limitations of this study include the small sample size and the lack of a placebo control. In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

Vitamin D

Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses.³³ Vitamin D supplements may increase the levels of T regulatory cells in healthy individuals and patients with autoimmune diseases; vitamin D supplements may also increase T regulatory cell activity.³⁴ In a meta-analysis of randomized clinical trials, vitamin D supplementation was shown to protect against acute respiratory tract infection.³⁵ However, in two double-blind, placebo-controlled, randomized clinical trials, administering high doses of vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the mortality rate when compared to placebo.^{36,37} High levels of vitamin D may cause hypercalcemia and nephrocalcinosis. The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. Ongoing observational studies are evaluating the role. At present there is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.

Zinc

Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses.³⁸ Zinc has been shown to enhance cytotoxicity and induce apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake in vitro.³⁹ The relationship between zinc and COVID-19, including

how zinc deficiency affects the severity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation.⁴⁰ Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids. Several clinical trials are currently investigating the use of zinc supplementation alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19. The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women. The doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily. However, there is currently insufficient evidence to recommend either for or against the use of zinc for the treatment of COVID-19. Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).^{41,42} Because zinc has not been shown to have a clinical benefit and may be harmful and there is insufficient evidence it is not recommended to use of zinc for the treatment of COVID-19 for long durations.

Anticoagulants and antiplatelets

Anticoagulants and antiplatelets should not be initiated for the prevention of venous thromboembolism(VTE) or arterial thrombosis if the patient who is not being admitted to the hospital, unless the patient has other indications for the therapy.⁴³ If anticoagulation is required Enoxaparin 1mg/kg once daily is the recommended dose.

Steroids

There is currently a lack of safety and efficacy data on the use of these agents, and systemic glucocorticoids may cause harm in these patients. Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions

In RECOVERY, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen. There was no observed benefit of dexamethasone in hospitalized patients who did not receive oxygen support.⁴⁴

Nonhospitalized patients who did not require supplemental oxygen were not included in this trial; thus, the safety and efficacy of corticosteroids in this population have not been established. Moreover, the use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. Dexamethasone was stopped at the time of hospital discharge during RECOVERY. For hospitalized patients with COVID-19 who do not require supplemental oxygen after discharge, it is advised to continue dexamethasone.

Remdesivir

Remdesivir is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. There is insufficient evidence for or against the use of Remdesivir in high risk patients with mild illness. All the recommendations and guidelines from MOHFW are against the use of Remdesivir at home.

Mild disease in pregnancy

Potentially effective treatments for COVID-19 should not be withheld from pregnant people because of theoretical concerns related to the safety of using those therapeutic agents in pregnancy. Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease. The use of anti-COVID-19 monoclonal antibodies can be considered in pregnant people with COVID-19, especially in those who have additional risk factors for severe disease. There is no pregnancy-specific data on the use of monoclonal antibodies; however, other immunoglobulin G products have been safely used in pregnancy when their use is indicated. Therefore, these products should not be withheld in the setting of pregnancy. To date, most SARS-CoV-2-related clinical trials have excluded individuals who are pregnant and lactating; in cases

where lactating and pregnant individuals have been included in studies, only a small number have been enrolled.

Concomitant Medication Management

Individuals with underlying medical conditions, such as cardiovascular disease, pulmonary disease, diabetes, and malignancy, are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions. It is unclear whether these concomitant medications have a positive or negative impact on the treatment and outcomes of COVID-19.

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19. Angiotensin-converting enzyme inhibitors, statin therapy, nonsteroidal antiinflammatory drugs, and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued. Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of COVID-19 Virus.

Empiric Broad-Spectrum Antimicrobial Therapy

In patients with severe or critical COVID-19, there is insufficient evidence to recommend either for or against empiric broad-spectrum antimicrobial therapy in the absence of another indication. If antimicrobials are initiated, it should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy. In specific situations, such as the presence of a lobar infiltrate on a chest X-ray, leukocytosis, an elevated serum lactate level, microbiologic data, or shock antimicrobials may be recommended.

Discharge

Patient under home isolation will stand discharged and end isolation after at least 10 days have passed from onset of symptoms (or from date of sampling for asymptomatic cases) and no fever for 3 days. There is no need for testing after the home isolation period is over.

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Management of Moderate and Severe Disease in Covid-19



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Severe acute respiratory syndrome corona virus-2(SARS-CoV-2) is highly infectious and cause for the pandemic worldwide since 2019. As the virus spread across the globe its manifestation, involvement of organs etc. was unfolding and even countries with the best of healthcare were found wanting. The WHO and country-specific guidelines to manage this disease emerged. The pharmacological agents were in and out within a short time ranging from allopathy to non-allopathy medications in our country.

Based on symptoms, clinical parameters cases were classified as mild, moderate and severe. Common symptoms ranged from cough, fever, throat pain, breathing difficulty, headache, malaise and body aches to less common like diarrhea, loss of smell and/ taste, skin rash etc. In a large cohort of 44,000 people with covid-19 from China, the severity of illness was mild to moderate (81%), severe (14%) and critical (5%).

Mild: symptoms without evidence of breathing difficulty or hypoxia.

Moderate: symptoms with Spo₂ less than 94% and respiratory rate less than 24/minute.

Severe: symptoms of breathing difficulty with Spo₂ less than 90% and respiratory rate more than 30/ minute.

CT-Chest: CORADS score

CORADS

- 1: normal
- 2: definitive diagnosis other than Covid
- 3: cannot definitively rule out Covid
- 4: suspicious of Covid
- 5: highly suspicious of Covid
- 6: RT-PCR positive

CT Chest severity score: mild disease 1-8; moderate 9-15 and severe 16-25.

Risk factors for severe disease: age >60 years, comorbidities-diabetes, hypertension, cardiac disease, chronic lung disease, chronic kidney disease, immune suppression and cancer.

The Ministry of health and family welfare (MOHFW) along with ICMR and AIIMS announced guidelines for managing cases based on severity. All suspected and proven cases of moderate and severe disease are to be admitted in designated covid hospitals.

Laboratory investigations: RT-PCR for suspected cases via nasopharyngeal or oropharyngeal swab and in those on mechanical ventilation preferably bronchoalveolar lavage (BAL) sample.

Bloods samples: CBP, CRP, Ferritin, IL-6, LDH, D-Dimer, renal function tests, LFT, procalcitonin (sepsis suspected), NT Pro BNP (heart failure), absolute neutrophil count and absolute lymphocyte count.

Daily 24 lead ECG

Radiological tests: Chest x-ray at admission and serially, CT-Chest were available in hypoxic patients and avoid repeating CT unless necessary.

Among the poor prognostic indicators elevated neutrophil lymphocyte ratio (NLR), low absolute lymphocyte count, high ferritin, CRP and D-Dimer.

Clinical management of moderate disease: hospital wards / room admission and monitored.

1. Symptomatic measures: anti-pyretic (paracetamol) for fever, cough (anti tussives), etc.
2. Hydration to be maintained.
3. Oxygen support: target Spo₂ (92-96%), those with COPD (88-92%). Devices used for

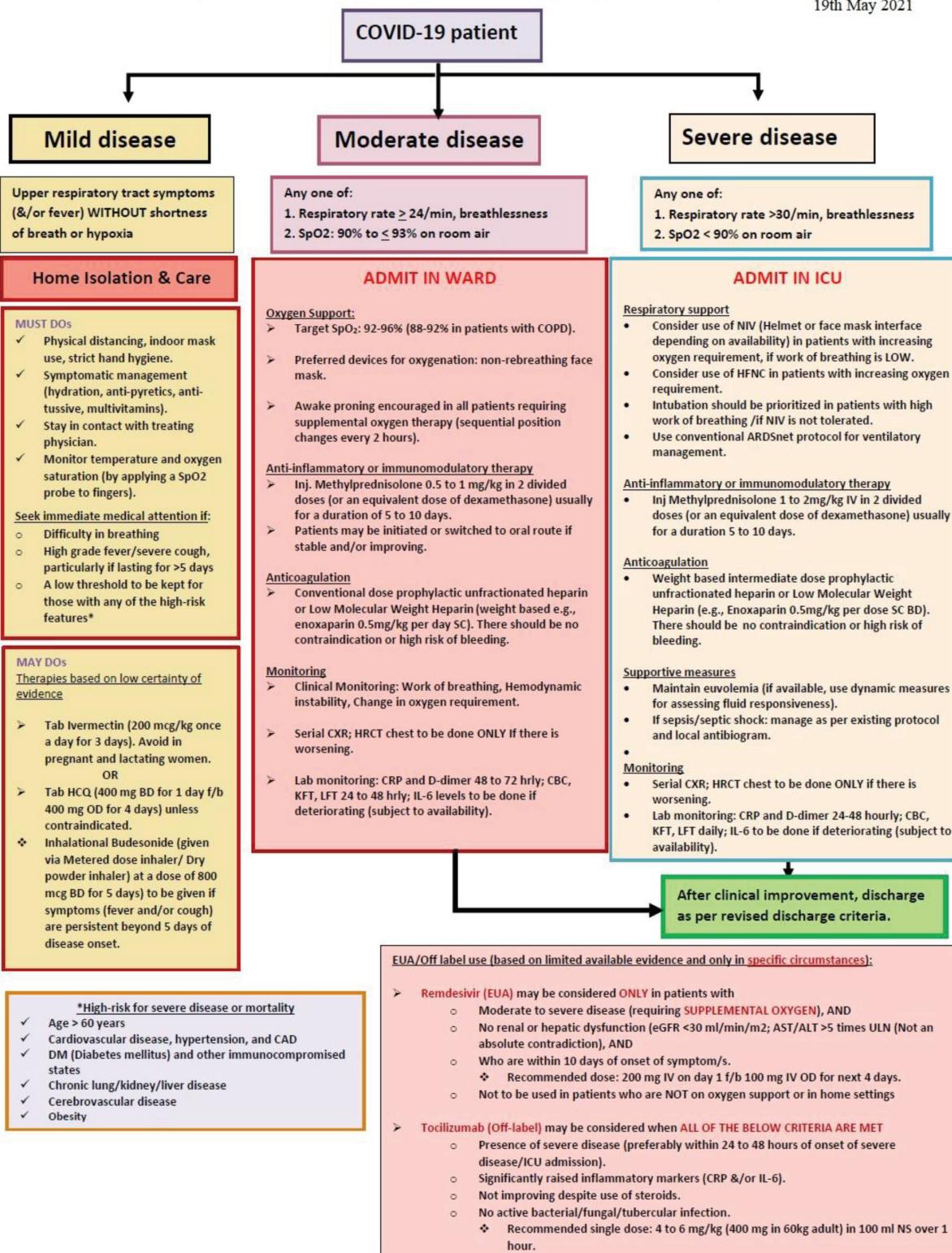


AIIMS/ ICMR-COVID-19 National Task Force/Joint Monitoring Group (Dte.GHS)

Ministry of Health & Family Welfare, Government of India

CLINICAL GUIDANCE FOR MANAGEMENT OF ADULT COVID-19 PATIENTS

19th May 2021



delivery of oxygen include nasal prongs, face mask, non-breather mask with reservoir etc. as increasing requirement.

4. Anti coagulation: prothrombotic state due to inflammatory cascade in covid-19, Un-Fractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH)eg: enoxaparin, to be added prophylactically.
5. Steroids: as anti-inflammatory/immuno modulatory therapy. Dexamethasone 6mg/day or equivalent dose of Methyl Prednisolone or Hydrocortisone 7-10 days to be used.
6. Awake proning: with sequential position change- most useful non-pharmacological intervention in covid-19 patients. Position change during awake times every two hours helped in ease of breathing and improved oxygenation.
7. Antibiotics recommended only where bacterial infection was suspected. Routine use of antibiotics to be avoided.

8. **Antiviral agents-**

Remdesivir is the only US-FDA approved anti viral agent in covid-19 cases. Initially emergency use authorization (EUA) given and the dosage was 200mg first day intravenously followed by 100mg once daily for 7 days and 10 days for those on mechanical ventilation. Current practice is to use for 5 days and stop as no significant benefit using for longer even in ventilated individuals.

Favipiravir has no proven benefit in hospitalized cases.

9. Baricitinib: a selective Janus kinase inhibitor, given orally inhibits the intracellular signaling pathway of cytokines. Also improves lymphocyte count and prevent entry of virus into the cell. Combined with Remdesivir reduces recovery time and accelerating improvement in clinical status of covid-19 patients. Recommended in those on oxygen and beyond.
10. Monitoring: work of breathing, hemodynamic stability, oxygen requirement, blood glucose

measurement.

11. Those who are worsening need shift to ICU and manage accordingly.

Management of severe disease: ICU admission

Individuals with breathing difficulty, Spo₂ <90% and respiratory rate >30/minute are classified as severe covid-19 disease.

1. Adequate hydration / euvolemic status
2. Respiratory support:

Oxygenation: target Spo₂ >90% (non-pregnant) and >92% in pregnant women

Non-invasive ventilation (NIV) to be commenced if work of breathing is more or Spo₂ is not maintaining. Interfaces used for NIV are orofacial mask / full face mask / helmet mask as tolerated by patient. Explain the purpose of NIV and what to expect while using NIV. Compliance, mental status and other organ functions should be monitored. Non-compliance, hemodynamic instability, altered mental state and multi organ failure if present invasive ventilation to be considered. Psychological support is very important especially for common man in ICU setting with gadgets, various sounds and sick patients around. NIV settings: PS 5-15cm H₂O, FiO₂-0.5-1 and PEEP 5-10cm H₂O. When higher PEEP was used pneumo-mediastinum and pneumothorax incidence increased.

High Flow Nasal Canula (HFNC): reduces the risk of progression to invasive ventilation. A few patients tolerate HFNC better than NIV as feeding, talking etc. is not hindered. Start with flow rates 20-30L/min and FiO₂ 0.5 onwards. Flow rates increased by 5-10L/min depending on work of breathing, SpO₂ and respiratory rate. If increasing flow alone doesn't achieve the target SpO₂ then FiO₂ increased up to 100%. Close monitoring needed for these patients.

Invasive ventilation: rapid sequential intubation appropriate as likelihood of de-saturation is high. Intubation preferably done by the senior most doctor available in the ICU. Use lower tidal volumes and lower inspiratory pressures and permissible hypercapnia (lung protective strategy for ARDS). Sedation is required for control of the respiratory drive and to achieve tidal volume targets.

Prone ventilation used in the event of refractory hypoxemia, $\text{PaO}_2/\text{FiO}_2 < 150$ with $\text{PEEP} > 5$ and $\text{FiO}_2 > 0.6$. Requires man power to prone and then supine, gel pads to protect the patient, unit should have the knowledge and experience of proning. Secure the tube and lines, also if needed turn back supine in the event of emergency. Prone ventilation should be performed for 16-18 hours in severe ARDS.

ECMO (Extra Corporeal Membrane Oxygenation) should be considered in refractory hypoxemia inspite of lung protective ventilation. Refer to a center where it is done regularly.

Medication:

Remdesivir- to use if less than 10 days from onset of symptoms, as no significant benefit beyond this period as viral replication ends by then in most individuals.

Steroids- Dexamethasone (0.2-0.4mg/kg) or Methylprednisolone (1-2mg/kg in two divided doses) are mainstay of treatment, duration 5-10 days.

Anti coagulation: unfractionated heparin or LMWH

Tocilizumab: IL-6 inhibitor used for suspected cytokine storm in those receiving steroids and worsening work of breathing, worsening oxygenation and raised inflammatory markers. Used within 24 hours of the above scenario is beneficial. Recommended single dose- 4 to 6 mg/kg (max 400mg)- as an infusion over one hour, after ruling out active tuberculosis and sepsis. Use of second dose of Tocilizumab was associated with poor outcome due to sepsis and activation of tuberculosis.

Bevacizumab: repurposed drug used when there was Tocilizumab shortage during the second wave. Almost similar to Tocilizumab used in many tertiary care centre's across the country.

Antibiotics-in only those with suspected bacterial infection, elevated procalcitonin and shock. Broad spectrum antibiotics to be started and cultures sent as relevant to guide duration and escalation and de escalation.

Shock: fluid resuscitation and if shock is not improved commence inotropes and vasopressors.

Monitoring:

CXR, CBP, RFT, LFT, LDH daily, CRP, d-dimer once in

3 days. IL-6 if clinical deterioration and cytokine storm suspected. IL-6 values are raised in cytokine storm and falsely positive due to processing etc. so only request for patients in ICU and severe disease.

Complications:

Pneumonia- ventilator associated- prevented by reducing ventilation days, weaning early

Pneumothorax / pneumomediastinum-low PEEP, low plateau pressure

Critical illness myo-neuropathy- mobilization (physiotherapy)

Venous thromboembolism- anti coagulation, stockings, DVT pumps, etc. as appropriate

Pressure ulcers: prevention by position change every second hourly.

Mucormycosis: second wave saw epidemic of Mucormycosis in few covid-19 cases, exact reason couldn't be ascertained but judicious use of steroids, glycemic control and infection control practices will reduce the cases.

One important factor of downtrend in severity of illness is vaccination, has definitely reduced number of deaths, severity of disease and hospitalization rates. Hopefully the successful vaccination of majority of adults will prevent the so called third wave.

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Background

COVID has created an extraordinary situation with unprecedented effects on us. Evidence is emerging and ever-changing. Amidst a cocktail of medications, micronutrients have been used, misused and abused in management of Covid.

Micronutrients (vitamins and trace elements) are needed in amounts <100 mg/day and are crucial in development, production and functioning of enzymes (Zinc, Copper, Manganese, Selenium, Magnesium, Molybdenum); hormones (Iodine, Chromium) and growth regulator proteins; reproductive and immune system; bone and membrane structure (Calcium, Phosphorus, Magnesium, Vitamin D); oxygen binding (Iron). There are several ways in which the immune system combats viral pathogens. First, it builds up barriers to prevent pathogens from entering the body. Secondly, the immune system identifies and eliminates pathogens. Thirdly, the immune system creates an immunological memory of the pathogen, allowing for rapid defense against that pathogen if the host encounters it again. Micronutrients are essential in all of the above processes. They contribute to the maintenance of the body's epithelial barriers, aid in the production of antimicrobial molecules, regulate the production of inflammatory cytokines that stimulate other parts of the immune system, assist in the maturation and proliferation of immune cells, inhibit the replication of viruses in the body, promote phagocytosis of infected cells, and stimulate the production of antibodies.

Role of Micronutrients in Covid

Vitamin C

Vitamin C is key for the integrity of the epithelial barrier, for the function of the leucocytes, the

macrophages, and the lymphocytes. Vitamin C promotes phagocytosis, contributes to the function of natural killer cells, and promotes production of antibodies. It is also a powerful antioxidant, which is important because phagocytic cells produce reactive oxygen species as part of their defense against infection. These reactive oxygen species can in turn damage immune cells, necessitating an adequate supply of antioxidants to neutralize the threat.

Although vitamin C supplementation doesn't reduce the risk of common colds, a metaanalysis found that it lowers risk of pneumonia, especially in people with low dietary intake of vitamin C. Supplementation also decreases the severity and duration of upper respiratory infections as well as the duration of mechanical ventilation and length of stay in the ICU (outside of the COVID-19 context). Preliminary observational studies suggest that critically ill patients with COVID-19 tend to have low vitamin C status, and one small trial from China found that vitamin C supplementation significantly decreased mortality in severely ill COVID-19 patients. There's some evidence that vitamin C supplementation decreases mortality by helping to prevent immune overreactions and cytokine storms, which are a component of severe COVID-19 cases. A small trial found that administering vitamin C (in combination with methylene blue and N-acetyl cysteine) decreased blood levels of multiple inflammatory cytokines in four of the five COVID-19 patients treated. Similarly, another study also found that IV administration of vitamin C (1 g every eight hours for three days) likewise reduced inflammatory markers. IV treatment with vitamin C has shown beneficial effects on sepsis, septic shock, and sepsis-induced acute respiratory distress syndrome, all of which are associated with COVID-19.

Though there is some evidence, it is not a recommendation in WHO or MOHFW guidelines to provide routine Vitamin C supplementation. It may be tried in immunocompromised patients.

Vitamin D

Vitamin D helps maintain the integrity of epithelial barriers in the body. It also stimulates production of antimicrobial peptides in lung membranes; such peptides have been shown to decrease replication of the influenza A virus. In addition, vitamin D aids the production of macrophage immune cells and increases phagocytosis. Finally, vitamin D regulates T cell responses and helps control the cytokine storms generated by the innate immune system in reaction to infections such as COVID-19.

Cross-sectional studies in the United Kingdom and the United States have found an inverse linear relationship between vitamin D levels and risk of respiratory tract infections. Different meta-analyses have found that supplementing with vitamin D decreases risk of respiratory tract infections.

In the context of COVID-19, a range of studies suggests that incidence and severity of the disease are linked with vitamin D status. Although an array of research suggests a link between vitamin D levels and COVID-19 incidence and severity, it's important to note a major exception to the pattern: An analysis of more than 500,000 participants in the UK Biobank study found that lower vitamin D levels were indeed linked to higher risk of infection but that this association disappeared after adjusting for confounding variables.²⁸

There's debate about whether the evidence justifies vitamin D supplementation in individuals who aren't deficient. However, it's worth noting that vitamin D deficiency is widespread, especially in older adults. For people with vitamin D deficiency as well as those at high risk of contracting COVID-19, Vit D supplements may be useful as an intervention.

Vitamin E

Vitamin E is a potent antioxidant, and it's present in high concentrations in immune cells to help protect cells from oxidative damage. Vitamin E deficiency reduces lymphocyte proliferation, the activity of natural killer cells, phagocytosis, and the production of antibodies. By contrast, vitamin E

supplementation has been shown across several studies to improve various markers of immune function.

In clinical studies, higher levels of plasma vitamin E are linked to lower risk of infections in adults over age. There is some thought that increasing vitamin E intake might be beneficial in the context of COVID-19, especially in older adults and those with heart complications. However, the evidence is limited, and there are no specific recommended dosages.

Zinc

Zinc has a very important role in the development and function of the macrophages and the immunoglobulins that are responsible for responding [to infection].²⁹ In addition to promoting the development of immune cells, zinc inhibits the replication of RNA viruses, including the SARS-CoV virus. Zinc deficiency also hinders phagocytosis, the activity of natural killer cells, and the production of T lymphocytes. Deficiency also spurs the production of inflammatory cytokines. Moderate doses of zinc were shown to reduce overproduction of inflammatory cytokines in older adults with zinc deficiency. Supplementation to correct a deficiency also has been shown to reduce the risk of skin infections and diarrhea.

Several systematic reviews and meta-analyses suggest that supplementing with zinc reduces the duration of the common cold, lowers risk of pneumonia in children, and decreases mortality when given to adults who have severe pneumonia.

No specific role of Zinc in COVID as per WHO or MOHFW Guidelines.

Take home message

Some experts believe the benefits of supplementation in the context of COVID-19 may outweigh the risks in certain cases, even for individuals without a deficiency. Supplementation with vitamins D and C as well as zinc may be beneficial for specific individuals in the context of COVID-19, either as a prophylactic measure or as a therapeutic treatment for individuals with the virus. However, we should proceed with caution when recommending supplements to patients, recognizing the limits of the available research and weighing the benefits against potential harms.



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COVID-19 is perhaps the first pandemic in human history for the treatment of which over 200 drug compounds have been tested and about 70 therapeutic agents subjected to clinical trials so far. Drugs that are under trial to treat COVID-19 range from minerals like Zinc to Monoclonal Antibodies like Casirivimab plus imdevimab to the most recent Stem Cell Therapy.

The immune-pathogenesis of severe COVID-19 as we understood now involves both virus-driven damage and an exuberant host inflammatory response, both contributing to acute lung injury, acute respiratory distress syndrome (ARDS), and multiple organ failure [1]. And hence drugs used in COVID-19 are either targeted against the virus or to suppress the host inflammatory response (Cytokine storm) or both in some cases.

The drugs used in COVID-19 can be broadly classified as

Antivirals

1. Remdesivir
2. Favipiravir
3. Lopinavir Ritonavir

Repurposed Antivirals

1. Ivermectin
2. Nitazoxanide
3. Hydroxychloroquine / Chloroquine
4. Doxycycline
5. Azithromycin

Immunomodulators

1. Corticosteroids
2. Interleukin 6 inhibitors
3. Interleukin 1 inhibitors

4. Kinase inhibitors (JAK, BTK inhibitors)
5. Colchicine
6. GM CSF Inhibitors
7. Intravenous Immunoglobulin (IVIG) therapy
8. Interferons (Alpha, Beta)

Anti SARS CoV 2 Antibody products

1. Convalescent Plasma
2. Anti SARS CoV 2 Monoclonal Antibodies
3. SARS CoV 2 specific IV IG

Cell-Based Therapy

1. Mesenchymal Stem Cell

Adjunctive treatment

1. Thromboembolism prophylaxis
2. Antibiotics
3. Zinc
4. Vitamin C
5. 2Deoxy glucose

SARS-CoV-2: Virology and Drug Targets

SARS CoV 2 is a positive-sense single-stranded enveloped RNA virus belonging to the Coronaviridae family, Nidovirales order, and Genus Betacoronavirus. These viruses are endemic respiratory and gastrointestinal viruses. Other viruses that belong to the Betacoronavirus genus include the MERS-CoV, SARS-CoV.

SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope.

The spike (S) protein of coronaviruses facilitates viral entry into human cells. Entry depends on binding

of the surface unit, S1, of the S protein to a cellular receptor, which facilitates viral attachment to the surface of target cells. In addition, entry requires S protein priming by cellular proteases, after priming S protein is lysed at the S1/S2 and the S2' site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit. SARS-S protein engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor and employs the cellular serine protease TMPRSS2 for S protein priming (2-4). TMPRSS2 acts on the S2 subunit, facilitating fusion

of the virus to the cell membrane. The virus then enters the cell. Inside the cell the viral RNA is released from endosomes by acidification or the action of an intracellular cysteine protease, cathepsin. Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase (RdRp). Structural proteins are synthesized followed by assembly and release of viral particles utilizing host Endoplasmic reticulum and Golgi Complex. These viral lifecycle steps provide potential targets for drug therapy.

S protein of SARS Co V 2 binds with
ACE 2 receptor present
on type 2 pneumocyte and nasal epithelial cells



Ivermectin, Doxycycline, Arbidol,
Anti SARS CoV 2 Antibody
products blocks S protein
thereby blocking this step

TMPRSS 2 / furin is activated that primes S protein



Azithromycin, Camostat

S protein is cleaved into S1 and S2,

S2 protein fuses with human cell membrane



HCO

Viral genome enters human cells by endocytosis



Remdesivir,
Lopinavir/Ritonavir,
Favipiravir, Doxycycline

Transcription of viral RNA, synthesising RdRp



Viral structural protein are synthesised on Endoplasmic Reticulum



Azithromycin, Ivermectin

These viral progeny is finally transported via golgi complex to cell membrane and it is exocytosed into extra cellular space

Figure 1 depicts life cycle of virus and potential targets of therapy used in COVID 19

In this chapter, we will be discussing pharmacology and rationale of use of Ivermectin, Hydroxychloroquine, Colchicine, Antibiotics, and 2 deoxyglucose in COVID-19.

Ivermectin:

Ivermectin is a macrocyclic lactone 22,23-dihydroavermectin B produced by the bacterium *Streptomyces avermitilis*. It is FDA approved for the treatment of several tropical diseases, including onchocerciasis, helminthiases, and scabies.

Ivermectin's antiviral properties have been documented towards several RNA viruses, including human immunodeficiency virus (HIV)-1, influenza, flaviviruses such as Dengue and Zika, and most notably, SARS-CoV-2 (COVID-19). (5, 7-9)

The proposed mechanism of antiviral activity of Ivermectin is as follows

1. It binds to and inhibits the transport function of the host importin α (IMP α) protein. IMP α is a known importin to mediate nuclear import of various viral proteins and key host factors. (5)
2. It may interfere with the attachment of the SARS-CoV-2 spike protein to the human cell membrane. (6)
3. Other mechanisms include inhibition of SARS-CoV-2 3CLPro activity (10, 11) (a protease essential for viral replication)
4. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19 (12-14).
5. Hemagglutination via viral binding to sialic acid receptors on erythrocytes is a recently proposed pathologic mechanism (15) of COVID-19 that would be similarly disrupted by ivermectin

A randomized, double-blind, placebo-controlled trial from Bangladesh (16) showed that a 5-day course of ivermectin resulted in an earlier clearance of the virus compared to placebo ($p = 0.005$), also the levels of inflammatory markers were lower at day 7 in ivermectin group. Similar results were

observed in a randomised trial using a combination of Doxycycline and ivermectin. Doses used were Doxycycline 100mg twice daily for 5 -10 days, and ivermectin 200mcg/kg per day 2-3 days (17). Recently a meta-analysis concluded with moderate certainty that large reductions in COVID-19 deaths are possible using ivermectin and using it early in the clinical course may reduce numbers progressing to severe disease. (18)

In guidelines published by Ministry of health and family Welfare (MOHFW) (19), ivermectin is recommended for the treatment of mild cases COVID-19 not requiring hospitalization. The dose of ivermectin used is 200mcg/kg per day for 5 days. Treatment should be started as early as possible. There are on-going trials to assess the role of ivermectin in post-exposure prophylaxis. It can be used in children weighing more than 15 kg. Animal studies have shown teratogenic effects and hence it to be avoided during pregnancy. Ivermectin is generally a well-tolerated drug, Adverse effects may include dizziness, pruritis, nausea, or diarrhoea.

ANTIBIOTICS

Doxycycline

Doxycycline is a broad-spectrum tetracycline-class antibiotic used in the treatment of infections caused by bacteria and certain parasites. It is proposed to be used in COVID-19 both due to its anti-viral and anti-inflammatory properties. The antiviral property of doxycycline has been previously demonstrated against Japanese encephalitis virus, Chikungunya virus, Dengue virus, and Respiratory Syncytial Virus.(20) It has shown to inhibit SARS-CoV 2 virus in vitro studies at a concentration of 4-5 millimol/L.(21)

The different mechanisms by which doxycycline acts as antiviral are as follows

1. Doxycycline binds to S protein of SARS CoV2 thereby preventing viral entry into the cell. (22)
2. Doxycycline inhibits viral replication by inhibiting zinc containing Matrix Metalloproteinases (MMP). (23)
3. It increases intracellular zinc finger antiviral

protein (ZAP). ZAP binds with viral RNA and inhibits viral growth. (24, 25)

4. Additionally, doxycycline also inhibits viral RNA-dependent RNA polymerase (RdRp). (26)

Doxycycline has a potent anti-inflammatory property. It reduces pro-inflammatory cytokines (IL-6, IL-8, and tumor necrosis factor (TNF)- α) subsiding the cytokine storm. It decreases nitrous oxide production (27) and inhibits matrix metalloproteinase-9, (28, and 29) which has a role in acute respiratory distress syndrome. Apart from this doxycycline can also treat secondary bacterial infection. (Fig 2)

It is not used as a stand-alone antiviral. With ivermectin, it has shown faster viral clearance and reduced the risk of hospitalization (16, 17). Doxycycline has been used as a specific treatment for COVID-19 in Brazil (30). In India it is not included in national guidelines, however, it is included in COVID kit for home treatment in many states (31). In the UK, national guidelines recommend doxycycline for suspected COVID-19 pneumonia in patients at high risk of adverse outcomes in the community, or if bacterial infection is suspected (32).

WHO and the US Center for Disease Control and Prevention recommend antibiotics for suspected bacterial pneumonia in COVID-19, with doxycycline included in the treatment guidelines for community acquired pneumonia (33–35)

Doxycycline is given in a dose of 100mg twice daily for 5 days. It causes discoloration of teeth and inhibits bone growth hence should be avoided in children less than 8 years of age. It is also contraindicated during pregnancy. Oesophagitis is a common side effect of doxycycline, if not appropriately managed it may cause mediastinitis. Doxycycline absorption is decreased when taken concurrently with an antacid, iron tablets, and laxatives. These medications should be avoided or carefully dosed.

Azithromycin

Azithromycin is a synthetic macrolide antibiotic effective against a broad range of bacterial and mycobacterial infections. Due to an additional range of anti-viral and anti-inflammatory properties, it has been given to patients with the coronaviruses SARS-CoV or MERS-CoV. It is now being investigated as a potential candidate treatment for SARS-CoV-2. Azithromycin reduces in vitro replication of several

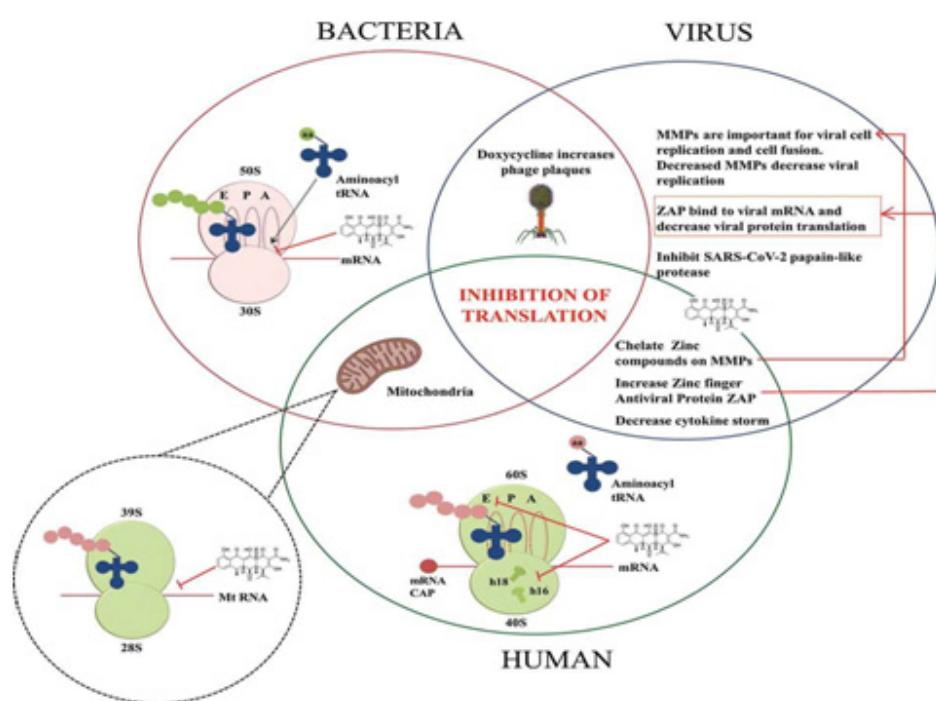


Figure 2 : Mechanism of action of doxycycline. Doxycycline increases ZAP, inhibits papain like protease of SARS CoV 2 hence inhibiting viral replication. In humans it inhibits MMP thus inhibiting inflammation. Its antibiotic efficacy is based on its ability to inhibit 30s ribosome of bacteria

classes of viruses including rhinovirus, influenza A, Zika virus, Ebola, enteroviruses, and coronaviruses (36), via several mechanisms.

1. Azithromycin acts by increasing the pH of the Golgi network and recycling endosome, (37) which interfere with intracellular SARS-CoV-2 activity and replication.
2. It also reduces levels of the enzyme furin, (37) thus inhibiting viral entry
3. Azithromycin also has anti-inflammatory properties including suppression of IL-1beta, IL-2, TNF, and GM-CSF. It inhibits T cells by inhibiting calcineurin signalling, mammalian target of rapamycin activity and NF- κ B activation.

Azithromycin particularly targets granulocytes where it concentrates markedly in lysosomes, particularly affecting accumulation, adhesion, degranulation, and apoptosis of neutrophils. Since azithromycin targets granulocytes, concentration at infection site is 50 times higher than in plasma. The combination of hydroxychloroquine and azithromycin has shown synergistic inhibition of SARS CoV2 in Vero cells (38). A small open label non-randomized clinical trial has shown early viral clearance with azithromycin and hydroxychloroquine combination compared to standard care group. (39) However, this combination failed to show mortality benefit in hospitalised patient.

It is given in a dose of 15 mg/kg per day up to a maximum of 500 mg per day. It is acid-stable and better absorbed empty stomach. Diarrhoea is the most common side effect. Nausea and abdominal pain are seen in less than 3% of patients. It prolongs the QT interval. The effect is more common in patients with low potassium or magnesium. Regular monitoring of QT is advisable when azithromycin is combined with other QT prolonging drugs like Remdesivir, Hydroxychloroquine or Fluroquinolones like levofloxacin.

Hydroxychloroquine:

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune

diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria.

Chloroquine, an analog of quinine, was known to inhibit the acidification of intracellular compartments [40] and has shown in vitro and in vivo (mice models) activity against different subtypes of Coronaviruses: SARS-CoV-1, MERS-CoV, HCoV-229E and HCoV-OC43 [41 -46]. In 2004 it was tested in vitro against SARS-CoV [47] and caused a 99% reduction of viral replication after 3 days. In recent in vitro study chloroquine has shown inhibit viral replication of SARS-CoV 2 [48].

Hydroxychloroquine (hydroxychloroquine sulfate) has shown activity against SARS-CoV2 in vitro and exhibited a less toxic profile [49]. Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesized to be another potential mechanism of action for the treatment of COVID-19. Azithromycin, when used in combination with hydroxychloroquine, has been shown to have a synergistic effect on SARS-CoV-2 in vitro and in molecular modelling studies.

HCQ received EUA in April 2020 for use in COVID-19 patients; however approval was revoked in June 2020 after the publication of interim reports of the Solidarity trial. In the guidelines published by MOHFW India, HCQ is recommended both for prophylaxis in high risk groups and also for treatment of mild COVID cases not requiring hospitalization (19, 50).

The dose of HCQ used in COVID-19 is 400mg per day. ECG should be done and QTc should be checked before starting HCQ therapy. HCQ should be avoided if QTc is more than 450msec in males and more than 470msec in females. Regular monitoring of QTc is recommended. Electrolyte abnormalities should be corrected and co-administration of QTc prolonging drug should be avoided.

Colchicine:

Colchicine is an alkaloid derived from the plants Colchicum autumnale and Gloriosa superba. Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions including acute gout, recurrent pericarditis, Behcet disease, prevention of

stroke, IgA Vasculitis and familial Mediterranean fever. (51-55) In addition, clinical studies support its cardioprotective effects and its beneficial effects in atherosclerosis and myocardial infarction, (56 - 58)

It has been proposed that colchicine can alleviate COVID-19 induced myocarditis primarily through inhibition of NLRP3 inflammasome (59, 60). Colchicine is under extensive investigation for its cardio-protective potential in COVID-19 patients. The COLCORONA trial showed that colchicine may reduce the composite rate of death or hospitalization by preventing the phenomenon of "cytokine storm" and subsequently reducing the complications arising from COVID-19 (61). The study results have shown that colchicine reduced hospitalization by 25%, need of mechanical ventilation by 50% and death by 44% compared to placebo.

Colchicine is a lipophilic drug with oral bioavailability around 45%. The drug is quickly taken up by leukocytes and hence concentration in leukocyte is more than that in plasma. It has a very narrow therapeutic window. The recommended dose of colchicine is 1mg per day in two divided doses.

Adverse effects include diarrhoea, neutropenia. A higher dose may cause bone marrow suppression leading to pancytopenia. Rhabdomyolysis and hair loss may occur in case higher doses are used for a prolonged period. Colchicine is metabolised by CY3A4. Concentration of colchicine increases when combined with CY3A4 inhibitors like azithromycin, ketoconazole, lopinavir. Fatal interactions are reported with erythromycin and clarithromycin.

2-Deoxy-D-glucose

2-Deoxy-d-glucose is a glucose molecule which has the 2-hydroxyl group replaced by hydrogen so that it cannot undergo further glycolysis. 2DG is phosphorylated by hexokinase to 2 deoxy glucose 6 phosphate (2DG-P). 2DG- P cannot participate in further steps of glycolysis and also it competitively inhibits the production of glucose-6-phosphate (62).

2-DG is uptaken by the glucose transporters of the cell. Therefore, cells with higher glucose uptake, for example, tumor cells, also have a higher uptake of

2-DG and it is being evaluated for the treatment of many cancers. (63)

Its role in COVID-19 is based on its ability to inhibit cell growth. Uptake of 2DG is higher in virus-containing cells and inflammatory cells that require higher energy. And hence it is proposed to exhibit both anti-inflammatory and anti-viral property. It is indicated in moderate to severe COVID-19 patients, who are hospitalized. It is given orally at a dose of 45mg per kg per dose twice daily for 10 days. It is available in sachet form. Each sachet containing 2.34 grams in powder form. 1 or 2 sachet is to be diluted in 100ml water and the amount of water to be given according to body weight. (64)

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INTRODUCTION

Coronavirus are medium-sized enveloped positive stranded RNA viruses whose name derives from their characteristic crown like appearance in electron micrographs. These viruses have the largest known viral RNA genomes with the length of 27 to 30 kb. The host derived membrane is studded with glycoprotein spikes and surrounds the genome which is encased in a nucleocapsid that is helical in its relaxed form but assumes a roughly spherical shape in the virus particle. Replication of viral RNA occurs in the host cytoplasm by a unique mechanism in which RNA polymerases binds to ladder sequence and then detaches and re-attaches at multiple locations allowing for the production of a nested set of m-RNA molecules with common 3 ends (20). Various anti-viral drugs have been evaluated in a register clinical trials for COVID-19 like favipiravir, oseltamivir, plasma treatment, hydroxychloroquine, chloroquine, umifenovir, remdesivir lopinavir/ritonavir etc.

In just six months the world's largest randomised controlled trial on COVID-19 therapeutics has generated conclusive evidence on the effectiveness of repurposed drugs for the treatment of COVID-19. Interim results from the Solidarity therapeutics trial coordinated by the World health Organisation, indicate that Remdesivir, hydroxychloroquine, Lopinavir/Ritonavir and interferon regimens appeared to have little or no effect on 28 day mortality or the in hospital course of COVID-19 among hospitalised patients.

The study which spans more than 30 countries looked at the effects of these treatments on overall mortality initiation of ventilation and duration of hospital stay in hospitalised patients. Other uses of the drugs for example in treatment of patients in

the community or for prevention would have to be examined using different trials. The WHO has announced the next phase in its Solidarity trial (Solidarity plus) which will enrol hospitalised patients to test three new drugs namely artisunate, Imatinib and Infliximab in hospitalise COVID-19 patients. Anti-viral medication provide maximum benefit when used early in the disease course. Last year data from clinical trials demonstrated the benefit of remdesivir in patients hospitalised with Covid 19 even when not yet requiring oxygen. The latest data show remdesivir's potential to help high-risk patients recover before they get sicker and stay out of the hospital all together.

Following schematic diagram shows different mechanisms of actions of different anti-viral drugs working at different locations in viral entry and it's replication. (Fig. Pls. see on Color pages section)

Lopinavir/Ritonavir

Following are the different clinical trials apart from the WHO run SOLIDARITY trial which have all shown no efficacy and mortality benefit with the use of LPV/r against COVID-19. (Table 1)

Favipiravir

Favipiravir is an RNA-dependent-RNA polymerases inhibitor approved for the treatment of novel influenza viruses in Japan and China and exhibits anti-viral activity across a wide range of RNA viruses. As SARS CoV2 is a single-stranded RNA virus RdRp represents a relevant target for the known mechanism of action of favipiravir. Only a few favipiravir efficacy trials in Covid-19 have been reported in the literature to date including two comparative trials in which favipiravir showed an advantage over other antivirals (Cai et all 2020; Chen et all 2020; Doi et all 2020; Sanders et all 2020;

Ivashchenko et all 2020). Numerous other favipiravir COVID-19 trials are ongoing or as yet unreported (Agrawal et.al 2020). Initial reports from China suggested that more than 80% of those infected with SARS CoV2 will experience mild or moderate disease yet few studies to-date have investigated therapeutic interventions in this population. In a company sponsored study published in international Journal of infectious diseases in November 2020, by Udwadia et all represent results of a randomised, comparative, open label, parallel group clinical trial to evaluate the efficacy and safety of oral favipiravir monotherapy in addition to standard supportive care as compared to standard supportive care alone in patients with mild to moderate Covid-19. It concludes, the lack of statistical significance on the primary endpoint was confounded by limitations of the RTPCR assay, but there is significant improvement in time to clinical cure suggests favipiravir maybe beneficial in mild to moderate COVID-19.

Remdesivir

Remdesevir is a novel nucleotide analogue that directly inhibits viral replication of SARS COV-2 by targeting the viral RNA polymerases inside of the cell(3). On entering the body, it is transformed into the active metabolite remdesivir triphosphate which is then incorporated into the viral RNA and stops replication of the virus within the host cell. No known variations have significantly altered the viral RNA polymerases has in vitro activity against SARS-CoV-2. It is used for hospitalized patients with severe COVID-19 because considerable data suggest it may reduce time to recovery, which is regarded as a clinical benefit. Among patients with severe disease, prioritize remdesivir for those requiring low-flow supplemental oxygen because it may also reduce mortality in this population. However, the optimal role of remdesivir remains uncertain, and some guidelines panels (including the World Health Organization) suggest not using it in hospitalized patients because there is no clear evidence that it improves patient-important outcomes for hospitalized patients (eg, mortality, need for mechanical ventilation). Other guidelines panels, including the IDSA & NIH, suggest using remdesivir in hospitalized patients who require supplemental

oxygen(6,8,14,15,16,33).

The USFDA approved remdesivir for hospitalized children>12 years and adults with COVID-19, regardless of disease severity. The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO). If a patient is otherwise ready for discharge prior to completion of the course, it can be discontinued. The pharmacokinetics of remdesivir in the setting of renal impairment are uncertain, and it is prepared in a cyclodextrin vehicle that accumulates in renal impairment and may be toxic; thus, Remdesivir is not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m² unless the potential benefit outweighs the potential risk(1,2,24). Given the short duration of therapy and the low concentration of the cyclodextrin vehicle, the risks in patients with renal impairment may be relatively low, and case series have reported safe use of Remdesivir in patients with acute kidney injury and chronic kidney disease. Liver enzymes should be checked before and during Remdesivir administration; ALT elevations >10 times the upper limit of normal should prompt discontinuation of remdesivir. Remdesivir should not be used with hydroxychloroquine or chloroquine because of potential drug interactions(12,13,31,32).

The risk of severe illness from COVID-19 infection is increased in pregnant patients. Also the risk of adverse pregnancy outcomes may also occur in COVID-19 positive patients with symptomatic infection like, pre-term birth, pre-eclampsia, coagulopathy and stillbirth. Pregnant patients with symptomatic COVID-19 infection are more likely to require ICU admission mechanical ventilation and ventilatory support/ ECMO compared to non-pregnant symptomatic patients. Remdesivir is approved for the treatment of COVID-19 in pregnant women. (Burwick 2020, Lampejo 2021, Nasrallahet al 2021 and 25,26,27,28)."

Efficacy of remdesivir has been evaluated for both severe and non-severe COVID-19 in hospitalized patients. In Severe COVID-19 Overall, data from randomized trials do not demonstrate a clear, major clinical benefit with Remdesivir alone among

Table1: Trials of Lopinavir/Ritonavir against COVID-19

Lopinavir/Ritonavir±Arbidol	Deng, L. et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. <i>J. Infect.</i> (2020) doi:10.1016/j.jinf.2020.03.002.3	Retrospective cohort study with control arm	Cohort	Outcome	Quality of study
Lopinavir/Ritonavir	Ye, X.-T. et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. <i>Eur. Rev. Med. Pharmacol. Sci.</i> 24, 3390–3396 (2020).4	Cohort study with control arm	Patients: 47 with COVID-19 infection Intervention: Lopinavir/Ritonavir (n=42) vs. standard therapy (n=5) Comparator: Contemporary controls	Results: Both groups achieved good therapeutic effect. Time to clinical recovery: Return to normal body temperature in a shorter time (test group: 4.8 ± 1.94 days vs. control group: 7.3 ± 1.53 days, $p=0.036$). Viral clearance faster in the Lopinavir/Ritonavir group than in the control group (test group: 7.8 ± 3.09 days vs. control group: 12.0 ± 0.82 days, $p=0.02$)	Very low
Lopinavir/Ritonavir	Cao, B. et al. A Trial of Lopinavir– Ritonavir in Adults Hospitalized with Severe Covid-19. <i>N. Engl. J. Med.</i> 38, null (2020). ²	RCT	Participants n=199, Hospitalized adult patients with confirmed SARS-CoV-2 severe infection. Oxygen saturation of <94% on ambient air or of $\text{PaO}_2/\text{FiO}_2$ of <300 mmHg. Intervention n=99, Lopinavir-ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, Comparator n=100 Standard care alone	Outcome -Primary endpoint: Time to clinical improvement, defined as an improvement of 2 points on a 7-category ordinal scale or discharge from the hospital No difference in time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI] 0.90 to 1.72). Mortality at 28 days was similar (19.2% vs. 25.0%; difference, -5.8 percentage points; 95% CI, -17.3 to 5.7). Viral clearance similar In a modified intention-to-treat analysis: Lopinavir-ritonavir led to a median time to clinical improvement that was shorter by 1 day (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Serious adverse events were more common in the standard- care group.	Moderate

hospitalized patients. In a meta-analysis of four trials that included over 7000 patients with COVID-19, Remdesivir did not reduce mortality (OR 0.9, 95% CI 0.7-1.12) or need for mechanical ventilation (OR 0.90, 95% CI 0.76-1.03) compared with standard of care or placebo. Meta-analyses, however, have pooled patients requiring various levels of oxygen support, and some data suggest that there may be

a benefit (faster recovery and possible mortality reduction) for a select subgroup of patients, specifically those with severe disease who only require low-flow supplemental oxygen. In an interim report of the WHO-sponsored, multinational SOLIDARITY trial of patients hospitalized with COVID-19, there was no difference in overall 28-day mortality between the 2750 patients randomly

assigned to open-label Remdesivir and the 2708 patients assigned to standard care (RR 0.95, 95% CI 0.81-1.11) [5,6]. In an accompanying meta-analysis that included data from SOLIDARITY and the trials discussed below, there appeared to be a trend toward lower mortality with remdesivir among those who were not on mechanical ventilation at baseline, but this did not reach statistical significance (RR 0.8, 95% CI 0.63-1.01). There was no mortality benefit among those on ventilation at baseline (RR 1.16, 95% CI 0.85-1.60).

ACTT-1, a multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) included 1062 patients with confirmed COVID-19 and evidence of lung involvement; 85 percent had severe disease and 27 percent were receiving invasive mechanical ventilation or ECMO at baseline. Remdesivir resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care (median 10 versus 15 days with placebo; rate ratio for recovery 1.29, 95% CI 1.12-1.49). Remdesivir reduced time to recovery whether patients were randomized within or after 10 days of symptom onset. However, in subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline. Among the subset of patients on mechanical ventilation or ECMO at baseline, the time to recovery was similar with Remdesivir and placebo (rate ratio for recovery 0.98, 95% CI 0.70-1.36), although it is possible that follow-up was too short to detect a difference. Overall, there was a trend towards lower 29-day mortality that was not statistically significant (11.4 versus 15.2 percent with placebo, hazard ratio 0.73, 95% CI 0.52-1.03). Among the subset of patients who were on oxygen supplementation but did not require high-flow oxygen or ventilatory support (either non-invasive or invasive), there was a statistically significant mortality benefit at that time point (4.0 versus 12.7 percent, HR 0.30, 95% CI 0.14-0.64).(4,34,35)

Although these trials evaluated 10 days of Remdesivir, 5 days of therapy may result in similar outcomes in patients who do not need mechanical ventilation or ECMO. In an industry-sponsored,

open-label randomized trial among nearly 400 patients who were hypoxic on room air or receiving non-invasive oxygen supplementation, the adjusted rates of clinical improvement and discharge by day 14 were comparable when remdesivir was given for 5 days versus 10 days. In a propensity analysis of a subset of participants in this trial, the adjusted clinical improvement rate was higher and the adjusted mortality rate was lower than those in a cohort of patients who had severe COVID-19 but did not receive Remdesivir. However, this comparison of patients from two separate studies should be interpreted with caution because of potential confounders in patient characteristics and management approaches that cannot be fully accounted for by the propensity analysis.

Among hospitalized patients with non-severe disease, remdesivir may have a modest benefit, but the clinical significance of the benefit is uncertain. In an open-label randomized trial, 584 patients with moderate severity COVID-19 (pulmonary infiltrates on imaging but oxygen saturation >94 percent on room air) were assigned to receive remdesivir for up to 5 days, Remdesivir for up to 10 days, or standard of care. By day 11, the five-day Remdesivir group had better clinical status according to a seven-point scale compared with standard of care (odds ratio 1.65, 95% CI 1.09 to 2.48). There was not a statistically significant difference at day 11 in clinical status between the 10-day Remdesivir group and the standard of care group. Although discharge rates by day 14 were higher with Remdesivir (76 percent in each of the remdesivir groups versus 67 percent with standard of care), these differences were not statistically significant. Interpretation of this trial is limited by the open-label design and an imbalance in co-therapies(15,18,22).

In ACTT-1, the large trial described above, remdesivir (given for up to 10 days) did not appear to reduce time to recovery among the 119 patients with mild-moderate disease (i.e. no hypoxemia or tachypnoea; five versus six days, recovery rate ratio 1.29, 95% CI 0.91-1.83), although the number of patients in that subgroup was underpowered to show a significant effect(7).

While remdesivir efficacy has been demonstrated in adults being treated for COVID-19, data in

paediatric patients are limited. The role of remdesivir in the treatment of COVID-19 in paediatric population is still evolving. Use in the context of clinical trial is recommended if possible, use outside of a clinical trial could be considered in hospitalised paediatric patients with an emergent or increasing need for supplemental oxygen, in consultation with a paediatric infectious disease specialist. In neonates weighing <3.5 kg, a very limited data is available; the optimal dose of remdesivir is not defined; for neonates weighing >/= 3.5kg, limited data is available. The loading dose would be 5 mg/kg on day 1, followed by 2.5 mg/kg/dose once daily in patients not requiring mechanical ventilation or extracorporeal membrane oxygenation(ECMO) has been recommended. Treatment duration is 5 days or until hospital discharge whichever is first. If patient does not improve clinically, 10 days treatment duration is recommended for patients who require mechanical ventilation or ECMO. However, some experts have suggested starting with a five day course and extending to 10 days on a case-by-case basis(11,17,18,29,30,33)

Reported side effects of remdesivir include nausea, vomiting, and transaminase elevations. In one trial, the most common adverse events were anemia, acute kidney injury, fever, hyperglycemia, and transaminase elevations; the rates of these were overall similar between Remdesivir and placebo. However, in another trial, remdesivir was stopped early because of adverse events (including gastrointestinal symptoms, aminotransferase or bilirubin elevations, and worsened cardiopulmonary status) more frequent than with placebo (12 percent versus 5 percent). Cases of bradycardia attributable to remdesivir have also been reported (10,11,19,21,23)

CASIRIVIMAB+IMEDIVIMAB

Casirivimab and Imedivimab are human IgG G1 (IgG1) monoclonal antibodies produced by recombinant DNA technology in Chinese hamster ovary cells. These are monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2 designed to block the virus attachment and entry into human cells these two distinct antibodies bind noncompetitively to the SARS N COV2 virus cell surface. It prevents virus from

infecting healthy cells. Using two antibodies protects against emergence of the resistance. These antibody cocktail are indicated for the treatment of mild to moderate COVID-19 adult patients and paediatric patients who are 12 years of age and older weighing at least 40 kg with the lab confirmed size SARS COV2 infection and who are at high risk of severe COVID19. The dosage for adult and paediatric patient (>12 yr of age+weight>40kg) is 600 mg of Casirivimab and 600 mg of Imedivimab administered together as a single IV infusion.. US FDA has issued an emergency use authorization for this antibody cocktail in November 2020. Other countries's FDAs (Germany, Italy, France, Sweden,Hungary, Denmark, Netherlands, Belgium, India, Estonia, Brazil etc) have also approved its use for indicated patients of COVID-19. There is no contraindication for its use except hypersensitivity including anaphylaxis and infusion related reactions which are very rare if anything is unrelated reaction or could consider slowing or stopping the infusion and administer appropriate medications and or supportive care. This Monoclonal antibody cocktail also has been approved for use to prevent infection in those patients who are vulnerable and don't have adequate antibody titers against SARS CoV2 and/ or have come in close contact with suspected or confirmed COVID-19 patients. These cocktails are seen to be effective in patients who don't have adequate antibody generation even after vaccination or prior infection as compared to those patients who have generated antibodies against SARS cov2. (36,37,38)

CONCLUSIONS:

Remdesivir is the drug of choice for CoVID 19 especially in (CatB) symptomatic patients if duration of symptoms is less than 7days. It can be used in neonates of age 6 months and above(5mg/kg loading dose followed by 2.5mg/kg.) and also in pregnant women safely wherever indicated.

Casirivimab Imdevimab antibodies cocktail is recommend in CoVID19 patients (CatA/CatB seronegative patients) and also in high risk primary contacts.

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Steroids in COVID-19

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COVID19 has arrived as a transformational pandemic. It has impacted all facets of human life, resulting in economic uncertainty, chaotic travel, overcrowded intensive care units, oxygen shortages and desperation in whole populations.

SARS-COV-2 is a coronavirus, not unlike various common cold coronaviruses. Based on T-cell response analysis, archaic humans may have dealt with a disease similar to COVID-19.¹

Therapies for COVID-19 have been developed through the rigorous application of evidence-based medicine (EBM) based on methodologically sound randomised clinical trials (RCTs). These have been incorporated by numerous national and international bodies /authorities to frame guidelines, thus, defining a standard of care.

Treatment of COVID-19 is focused on the resolution of a patient's symptoms, the prevention and treatment of complications, and ultimately, reducing long-term morbidity and mortality.

Treatment is guided by disease severity.

The World Health Organization(WHO)² has classified COVID-19 based on the clinical features into:

1. **Non-severe:** Absence of symptoms/signs of severe or critical disease
2. **Severe:** Peripheral oxygen saturation of less than 90% on room air or in addition to signs of pneumonia, signs of severe respiratory distress in adults or children. In adults, this is manifested as the use of accessory muscles of respiration, inability to complete entire sentences or tachypnea with a respiratory rate of greater than 30 breaths/min. In children, severe COVID-19 manifests as very severe chest wall indrawing, cyanosis or general

danger signs (inability to breastfeed or drink, lethargy, reduced level of consciousness or convulsions)

3. **Critical COVID-19:** This is defined as fulfilling acute respiratory distress syndrome (ARDS) criteria, sepsis, septic shock, or institution of invasive or non-invasive mechanical ventilation or vasopressor therapy.

The Covid Management Guidelines India Group³, a collection of senior expert clinicians, academics, and methodologists in reputed institutions nationally, has largely incorporated the WHO's classification but further subdivided non-severe COVID-19 into mild and moderate as follows:

1. **Mild COVID-19:** Symptomatic COVID-19 with no features of pneumonia (clinical/radiological) or hypoxia.
2. **Moderate COVID-19:** Symptomatic COVID-19 with clinical or radiologic features of pneumonia; no evidence of severe hypoxia ($\text{SpO}_2 < 90\%$ on room air) or respiratory distress (respiratory rate > 30 breaths/min). Mild hypoxia ($\text{SpO}_2 90-94\%$ on room air) and increased respiratory rate (24-30 breaths/min) are classified as moderate COVID-19 pneumonia.

The National Institutes of Health⁴ have classified the severity of disease into the following categories:

1. **Asymptomatic or Presymptomatic Infection:** Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test but have no symptoms.

2. **Mild Illness:** Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging.
3. **Moderate Illness:** Patients with lower respiratory disease by clinical assessment or imaging and oxygen saturation (SpO_2) $<94\%$ on room air at sea level.
4. **Severe Illness:** Individuals who have respiratory frequency >30 breaths per minute, $\text{SpO}_2 <94\%$ on room air at sea level, the ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) <300 mm of mercury or lung infiltrates $>50\%$
5. **Critical Illness:** Individuals who have respiratory failure, septic shock, or multiple organ dysfunction.

Given that 81% of patients have either no pneumonia or mild pneumonia⁵ (as defined by CT), supportive care with antipyretics, antitussives, analgesics forms the mainstay of treatment for most patients. Despite initial concerns regarding possible worse outcomes in patients given non-steroid anti-inflammatory drugs early in the course of disease⁶, they were not associated with worse results in one study⁷, and guidelines recommend their use if clinically indicated.⁴

In this article, the authors will summarise the evidence behind the recommendation to use steroids in severe COVID-19.

Steroids

- **Mechanism of Action**

Generally, a prednisone dose of less than 1 mg/kg body weight in children or less than 40 mg in adults is considered a low-moderate dose. Glucocorticoids result in neutrophilic leukocytosis, monocytosis, eosinopenia and lymphocytopenia.

Steroids result in a phenomenon called 'leucocyte trapping', resulting in a reduced ability of white blood cells to adhere to the vascular

endothelium and exit from the circulation. There is a reduced systemic inflammatory response as a result.

Glucocorticoids induce a T-cell and B-cell immune deficiency, although the effect on T-cells is more significant than on B-cells. They inhibit the production and signalling of IL-2, a principal T-cell growth factor, impair the release of T-cells from lymphoid tissues and promote apoptosis. Additionally, they inhibit the production of Th1-and Th2-derived cytokines by activated T-cells. Regarding B-cells, antibody production is largely preserved; however, large doses given acutely and longer courses of smaller doses cause hypogammaglobulinemia.

- **Evidence for steroids in COVID-19**

The RECOVERY trial⁸ is an ongoing multicentre, open-labelled, randomised controlled trial investigating several treatment options for hospitalised patients with COVID-19. In one of the arms, oral or intravenous dexamethasone was administered at 6 mg once daily for a maximum of ten days. In the dexamethasone group, mortality was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs 41.4%; relative risk, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs 26.2%; relative risk 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving neither oxygen support nor invasive mechanical ventilation at randomisation (17.8% vs 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55). Thus, the benefit of corticosteroids is maximal in the group receiving invasive mechanical ventilation at baseline, with a smaller magnitude of benefit in those receiving oxygen without invasive mechanical ventilation. Dexamethasone was associated with increased mortality rates (17.8% vs 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55) when administered in patients who were not receiving oxygen or other forms of respiratory support. This finding is the main reason for avoiding steroids in the first week

of illness (unless the patient is on oxygen therapy) as the trial showed increased mortality in those, not on oxygen. In COVID-19, the onset of hypoxia is usually after 5-7 days after symptom onset.

It would suffice to say that numerous systematic reviews and meta-analysis⁹⁻¹² that corticosteroids have a definite role and proven mortality benefit in patients on supplemental oxygen and other forms of respiratory support, with the most significant benefit seen in those who are critically ill- that is on invasive mechanical ventilation followed by those on non-invasive ventilation (NIV) /high-flow nasal oxygen (HFNO). The reader is referred to the above references for further in-depth reading.

The National Institutes of Health (NIH)⁴, Infectious Diseases Society of America¹³ (IDSA), World Health Organization² and the COVID India guidelines³ recommend oral or intravenous dexamethasone at a dose of 6 mg (this is 8mg sodium phosphate salt) once daily in patients receiving supplemental oxygen or other forms of respiratory support.). If dexamethasone is unavailable, methylprednisolone 32mg/day, prednisolone 40mg, or hydrocortisone 150mg /day can be used at an equivalent dose.

The dose of steroids recommended is 8 mg of dexamethasone once daily for up to 10 days, although higher doses and longer durations of treatment have been employed in ARDS and in COVID-19 in some studies. These are detailed below.

- **Corticosteroids in ARDS**

The dose and duration of steroids used in COVID-19 are significantly lower than the doses used in randomised clinical trials of patients with moderate-severe ARDS.¹⁴⁻¹⁶ The dose of steroids employed in these trials were:

1. Single-dose of 2 mg of methylprednisolone per kilogram of predicted body weight followed by a dose of 0.5 mg per kilogram of predicted body weight every 6 hours for 14 days, a dose of 0.5 mg per kilogram of

predicted body weight every 12 hours for seven days, and then tapering off the dose.¹⁶

2. Loading dose of 1 mg/kg followed by an infusion of 1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to day 21, 0.25 mg/kg/d from day 22 to day 25, and 0.125 mg/kg/d from day 26 to day 28.¹⁴
3. Dexamethasone 20 mg IV once daily for five days, then 10 mg once daily for five days.¹⁵

In two of these trials, steroids had a mortality benefit.^{14, 15} A study investigating individual patients' data from four randomised trials and a trial-level meta-analysis incorporating four additional RCTs which investigated hydrocortisone treatment in early ARDS found that prolonged methylprednisolone treatment results in faster ARDS resolution, improved clinical outcomes and mortality benefit.¹⁷

- **Inhaled corticosteroids**

Two studies have shown inhaled budesonide to have clinically significant benefits in non-hospitalised patients with COVID-19.

Published in The Lancet Respiratory Medicine, the **STERoids In Covid-19 (STOIC)** trial¹⁸ was a prospective, randomised, open-label, phase 2 trial that compared treatment with 1600 µg (two puffs of 400 µg to be taken twice per day) of inhaled budesonide versus usual care in 146 adults within seven days of the onset of mild COVID-19 symptoms. Seventy-three adults were randomly assigned to the budesonide group or placebo. The primary outcome of the trial was urgent care visits, including emergency department assessment or hospitalisation. Results showed that, in the per-protocol analysis, this primary outcome occurred in ten (14%) participants in the usual care group and one (1%) participant in the budesonide group (difference in proportions 0·131, 95% CI 0·043–0·218; $p=0·004$), indicating a relative risk reduction of 91% for budesonide; notably, the number needed to treat with budesonide to reduce COVID-19 deterioration was eight patients. Secondary outcome results showed that clinical recovery

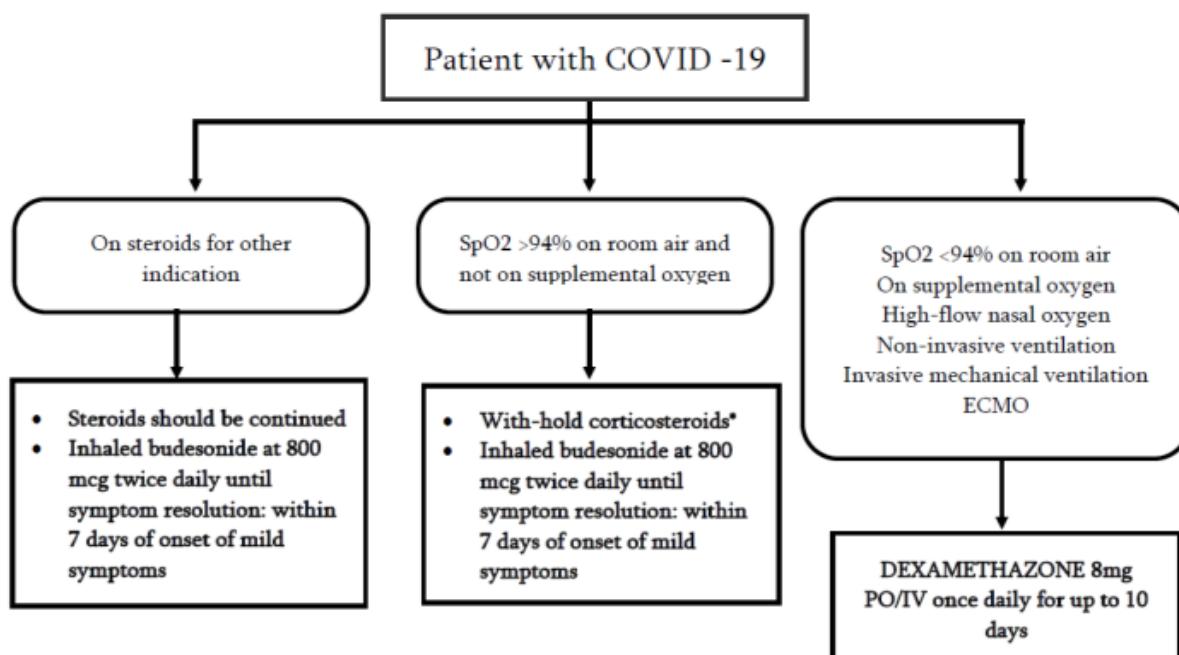
was also significantly reduced in the budesonide group. Based on these observations, the authors concluded that early administration of inhaled budesonide in patients infected with SARS-CoV-2 reduced the likelihood of needing urgent medical / hospitalisation and enhanced clinical recovery.

The PRINCIPLE trial¹⁹ is a United Kingdom-wide clinical study conducted by the University of Oxford to find effective outpatient treatments for COVID-19. It is a multicentre, open-label, multi-arm, adaptive platform. Participants were SARS-CoV-2 positive, age 65 or older, or aged more than 50 with comorbidities, symptomatic for 14 days or less but not hospitalised. Coprimary endpoints were time to self-reported recovery and hospitalisation or death due to COVID-19 within 28 days. As part of the PRINCIPLE trial¹⁹, 961 people were randomly assigned to receive inhaled budesonide at home and were compared with 1819 patients randomly assigned to the usual standard of NHS care alone.

Based on data collected up to March 25 2021, the interim analysis involved 751 people in the budesonide group (800 µg twice a day for 14 days) and 1028 in the usual care group SARS-CoV-2 positive. It found that the median time to self-reported recovery for people taking inhaled budesonide was 3.011 days shorter than usual care (95% Bayesian credible interval 1.134 to 5.410 days), with a high probability (0.999) of being superior to the usual standard of care. Data also showed that inhaled budesonide reduced the chance of hospitalisation or death due to COVID-19, although it did not meet prespecified superiority endpoints.

• High-dose systemic corticosteroids

One study showed that treatment of severe Covid-19 with high-dose methylprednisolone for three days followed by oral prednisone for 14 days, compared with 6 mg dexamethasone for 7 to 10 days, statistically significantly decreased the recovery time, the need for transfer to intensive care and the severity markers C-reactive protein (CRP), D-dimer and LDH.²⁰



*In absence of hypoxia, in exceptional circumstances, low dose steroids may be considered for the shortest possible duration in patients with fevers (with/without other symptoms) for more than 10 days, high CRP [>75 mg/dl] and other raised inflammatory markers.

A few case series have reported benefits with high-dose steroids.^{21, 22} It would, however, be worth noting that there are no high-quality data, that is, evidence from randomised clinical trials to guide the use of high-dose steroids in COVID-19. The RECOVERY trial is currently testing high-dose versus standard-dose corticosteroids.

Drug interaction with remdesivir

The University of Liverpool COVID-19 drug interaction checker mentions that a clinically significant interaction between low-dose dexamethasone and remdesivir is unlikely.²³ However, it is to be noted that the quality of evidence is very low as co-administration has not been studied,

Conclusion

In accordance with World Health Organization² and Covid Management Guidelines India Group³ guidelines, we have attached an algorithm regarding the use of inhaled and systemic steroids in patients with COVID-19.

Steroids have a definite role and proven mortality benefit in patients on supplemental oxygen and other forms of respiratory support, with the greatest benefit seen in those on invasive mechanical ventilation. Judicious use of the appropriate dose and duration of steroid for the correct clinical indication is most important. Certainly, patients with mild-moderate COVID-19 without hypoxemia should not be administered corticosteroids.

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Anticoagulants in COVID 19



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INTRODUCTION:

A novel coronavirus called severe acute respiratory distress syndrome coronavirus 2(SARS CoV2) causes the COVID 19 infection. This infection led to a global pandemic (1) contributing to significant mortality (2) worldwide. This infection predominantly affects the respiratory system manifesting from mild cough (3) and fever to respiratory distress (4) and hypoxia with mechanical ventilatory support. Primary respiratory failure is the leading cause of death (5). In addition, patients with severe infection develop hemostatic abnormalities (6), further complicating the course of the disease. This chapter discusses the problems associated with these hemostatic abnormalities and their management.

THROMBOEMBOLIC PHENOMENA IN COVID 19 INFECTION

The amount of literature demonstrating the association of thromboembolic manifestations and COVID-19 is expanding. The risk of developing these abnormalities was directly proportional to the severity of infection (7) with high venous thromboembolism (VTE) rates for acutely ill or hospitalized with COVID-19, including those receiving critical care. The incidence of thromboembolic manifestations is varied. A meta-analysis showed an incidence of deep venous thrombosis of 20%, pulmonary embolism of 13%, and systemic embolism of 2% in patients with severe COVID 19 (8).

Several investigators tried to understand the pathophysiology of a prothrombotic state in COVID-19.

a. Systematic inflammatory response:

An exaggerated inflammatory response occurs in severe COVID 19 infections (9).

Serum fibrinogen levels are upgraded, resulting in excess fibrin degradation products. The fibrinolytic system becomes impaired to clear these abnormal fibrin deposits, increasing their procoagulant activity. Platelet dysfunction and complement activation add to the insult and contribute to the development of a hypercoagulable state.

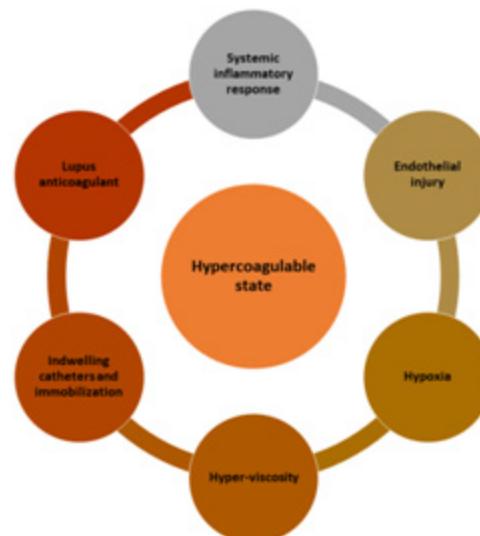


Figure 1: Various factors contributing to the hypercoagulable state in COVID 19

b. Endothelial injury:

SARS CoV2 enters the cell by binding spike glycoprotein on the surface of the viral envelope and angiotensin-converting enzyme 2(ACE2) receptors on the host cells. The surface of type II alveolar cells in the lungs and endothelial cells express ACE 2 receptors. Direct cellular injury mediated by the ACE2 pathway has evidence of elevated coagulation factors VIII and von Willebrand factor (vWF), soluble P-selectin, and soluble CD40L (10). The characteristic histological findings include disruption of endothelial cell membranes by

intracellular infiltration of the virus, thrombosis of the alveolar capillaries, and neo-angiogenesis. Collectively they lead to flow disturbance, interstitial edema, and thrombosis.

c. Development of anti-phospholipid antibodies:

Whenever cellular damage causes remodeling of the plasma membrane, microparticles are released, causing exposure to phospholipids. Antibodies developed against these phospholipids are called anti-phospholipid antibodies (aPL). Lupus anticoagulant, one of the aPLs, is elevated in patients with moderate to severe COVID 19 infection (11). Lupus anticoagulant can lead to both arterial and venous thrombosis. Coagulation parameters are deranged, and patients usually have prolonged activated partial thromboplastin time (aPTT). Therefore, patients with Lupus anticoagulant should receive anticoagulation despite prolonged aPTT(12).

d. Profound hypoxia:

Hypoxia in capillaries causes vasoconstriction, which can lead to occlusion, further aggravating hypoxia. In addition, hypoxia also leads to the release of hypoxia-inducible factors (HIFs) (13). These factors can induce or inhibit several genes which are actively involved in the coagulation cascade.

e. Hyper-viscosity:

There is evidence of hyper-viscosity causing cellular damage in few observational studies (14). It is one of the contributing factors promoting a hypercoagulable state.

f. Use of indwelling catheters and prolonged immobilization:

COVID 19 patients admitted to ICU can require continuous oxygen supplementation. Many of the patients require mechanical ventilation for managing hypoxia. In selected patients, extracorporeal membrane oxygenation (ECMO) helps in supporting oxygenation and circulation. Mechanical

ventilation, the use of indwelling venous and arterial catheters, and prolonged ICU stay further increases the risk of thromboembolism in severe COVID 19 patients (15).

MANAGEMENT

PROPHYLAXIS

The American Society of Haematology defines the target population as "acutely ill" and "critically ill" (16). Patients with COVID-19 who develop respiratory or cardiovascular failure typically requiring advanced clinical support in the ICU are "critically ill"; whereas those who don't need this support are "acutely ill." Several guidelines and societies recommend thromboembolic prophylaxis to all hospitalized patients (17,18,19,20). Patients with COVID 19 and elevated D-dimer levels have an increased risk of thromboembolic events (21). However, high D-dimers levels should not dictate the dose of anticoagulation or its escalation (18,20). In addition, it is essential to note that patients with COVID 19 have thrombotic risk despite prolonged aPTT (22).

Low molecular weight heparin (LMWH) or fondaparinux is the first choice for thromboprophylaxis. In patients having a high bleeding risk or reduced creatine clearance, unfractionated heparin (UFH) is the drug of choice. Usage of direct oral anticoagulants should be limited in the hospital setting as the clinical course of these patients is unpredictable. Also, there can be interactions with other drugs they are receiving as a part of treatment for COVID 19 pneumonia (23). There is no role of antiplatelets for thromboprophylaxis (24). Mechanical thromboprophylaxis (25) in the form of a sequential compression device (SCD) or graduated compression stockings is helpful in patients with high bleeding risk.

Prophylactic dose of drugs used for thromboprophylaxis:

- Unfractionated heparin 5000U SC BID; 7500U SC BID for BMI >40
- Fondaparinux 2.5mg SC OD
- Dalteparin 5000U SC OD

- Enoxaparin 40mg SC OD; 40 mg SC BID for e"BMI 40
- Apixaban 2.5mg PO BID
- Rivaroxaban 10 mg PO OD

Few prospective cohort studies have noticed residual thrombotic risk in patients receiving thromboembolic prophylaxis (22). However, there is an increased risk of bleeding with increased intensity of thromboprophylaxis regimens. Therefore, clinicians should avoid routine administration of an intermediate dose of thromboembolic prophylaxis as the clinical evidence favoring net clinical benefit is insufficient (20). Hence it is suggested to use an intermediate dose of thromboembolic prevention in highly selected individuals considering the risk-benefit ratio.

Intermediate dose of thromboprophylaxis:

- Unfractionated heparin 7500U SC TID
- Enoxaparin 40 mg SC BID for BMI <40; 60 mg SC BID for e"BMI 40
- Dalteparin 5000U SC BID

TREATMENT:

Management of a patient with a confirmed or suspected proximal deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE) is different.

Therapeutic dose of anticoagulants in COVID 19 infection:

- Unfractionated heparin 250U/kg SC q12h
- Fondaparinux
 - 5 mg SC OD if wt <50kg or CrCl 30-50ml/min
 - 7.5 mg SC OD if wt 50-100kg
 - 10 mg SC OD if wt >100 kg
- Dalteparin 100U/kg Sc BID
- Enoxaparin
 - 1mg/kg SC BID for CrCl > 30ml/min
 - 1mg/kg SC OD for CrCL< 30 ml/min
- Apixaban 5 mg PO BID
- Rivaroxaban 20 mg PO OD
- Dabigatran
 - 150 mg PO BID if CrCl > 30 ml/min
 - 75 mg PO BID if CrCl 15-30ml/min

- Acenocoumarol or Warfarin PO to target INR 2.0-3.0

Weight-adjusted LMWH is preferred to UFH as it has the advantage of avoiding additional laboratory testing and limits the use of personal protective equipment. However, in patients with high bleeding risk, severe renal failure, and hemodynamic instability, UFH is the drug of choice. Among the novel oral anticoagulants (NOACs), Apixaban and rivaroxaban are the first-choice, followed by Dabigatran. Vitamin K antagonists (VKA) with a target INR between 2.0-3.0 provide thromboprophylaxis in patients with reduced creatinine clearance. An overlap with initial parenteral heparin will follow the initiation of Dabigatran or VKA. LMWH benefits patients with recurrent VTE on oral anticoagulants, and for patients with recurrent VTE on therapeutic weight-adjusted LMWH, the dose of LMWH is increased by 25-30% (26).

MONITORING:

If not prolonged at the baseline, aPTT helps in monitoring the therapeutic efficacy of heparin. However, many patients with COVID 19 have prolonged aPTT and makes this parameter unreliable for monitoring. On the other hand, Anti-Xa assays are reliable and helpful in patients with prolonged aPTT (19).

LYTIC THERAPY:

Though few observational studies demonstrate improved oxygen status with thrombolytic therapy, there is no sufficient evidence to support the same (19). The indication for thrombolytic treatment includes patients who have established PTE and hypotension or other signs of obstructive shock and are not at high risk of bleeding.

DURATION OF ANTICOAGULATION

In patients with established proximal DVT or PTE, anticoagulant therapy is recommended for a minimum of three months (26).

POST-DISCHARGE THROMBOPROPHYLAXIS:

Epidemiologic data suggest that up to 80% of all hospitalization-associated VTEs occur after discharge (27). Unfortunately, there is no randomized controlled trial comparing the use of anticoagulation in patients discharged from hospital from COVID 19 infection. Therefore, routine

administration of oral anticoagulants for thromboprophylaxis after discharge is not advisable (18). However, the benefit of offering thromboprophylaxis should weigh the risks of bleeding it brings. Based on the information provided in popular guidelines, modified IMPROVE VTE (MIV) score, and D-dimer levels help risk-stratify the patients to receive post-discharge thromboprophylaxis (20). Patients having increased MIV score, D-dimer values will qualify to receive post-discharge prophylaxis.

The Scientific Position Statement by Heart Disease Management Program, released by National Health Mission, Government of Tamil Nadu, recommends the use of Padua risk assessment model (table 2) for risk stratifying VTE.(28)

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilization >1 day	1
Age >60 years	1

Table 1. Modified IMPROVE VTE risk score. A score of >4 or 2 or 3 with elevated plasma D-dimer levels indicates a high risk for VTE. Abbreviations: CCU—cardiac care unit, ICU-intensive care unit.

Risk factor	Score
Active cancer	3
Previous VTE	3
Reduced mobility	3
History of thrombophilic condition	3
Recent (< 1 month) trauma or surgery	2
Age >70 years	1
Heart or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection or rheumatological disorder	1
Obesity (body mass index >30 kg/m ²)	1
Hormone replacement therapy	

Table 2. Padua risk assessment model for VTE. A total score of >4 indicates a high risk of VTE.1

Direct oral anticoagulants are the preferred drugs because they do not require any tests to monitor their efficacy. FDA approves Rivaroxaban 10 mg PO OD for post-discharge thromboprophylaxis. Apixaban 2.5 mg PO BD is also a reasonable alternative. In patients with reduced creatinine clearance of < 15 ml/min/m², vitamin K antagonists should be used targeting an INR of 2.0-3.0. 30-45 days of thromboprophylaxis after discharge is considered adequate.

As antiplatelet agents help prevent atherosclerotic cardiovascular diseases (ASCVD), they should be continued in patients who are already using them. However, the addition of oral anticoagulants further increases the risk of bleeding. Therefore, a combination of antiplatelet agents and anticoagulants is avoided unless there is a compelling indication to use the same. When used, the duration of the therapy should not exceed more than one month.

ISSUES UNANSWERED:

The current evidence of literature supports the management of the hypercoagulable state in adults with COVID 19. However, management in particular categories like pregnant and lactating women and children is unclear. The currently available studies do not include this specific population. Therefore, their treatment is individualized, and a multi-specialty consultation will help take a calculated informed decision on anticoagulation.

CONCLUSION:

The severity of COVID19 infection is variable. Patients with moderate to severe illness can develop thromboembolic manifestations. Therefore, patients should be risk-stratified, and thromboembolic prophylaxis recommended after understanding the risk-benefit ratio. Low molecular weight heparin is the anticoagulant of choice unless there is a high bleeding risk, renal failure, or low body weight. Few selected patients will benefit from post-discharge anticoagulation for thromboprophylaxis. Rivaroxaban or Apixaban for 30-45 days is sufficient in most cases.

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Anti Sars-Cov-2 Specific Monoclonal Antibodies in the Management of Covid 19



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INTRODUCTION

The SARS-CoV-2 is a new virus causing corona virus disease 2019 (COVID-19). Despite the increasing use of highly effective vaccines, SARS-CoV-2 has not been eradicated. Moreover, it is unclear how many persons will ultimately choose to become vaccinated, how vaccine efficacy will wane over time, and how great a problem emerging variants of concern will be. As on date there are no specific antiviral drugs to treat SARS-CoV-2. For these reasons, a need will persist for a complementary approach to prevent the spread of SARS-CoV-2 infection in persons who are not vaccinated, who have waning vaccine-mediated protection over time or because of the emergence of variants, or who are immunocompromised and cannot mount an antibody-mediated antiviral response. The neutralizing titres achieved with Antibody cocktail were more than 1000 times the titres achievable with convalescent-phase plasma. Anti SARS-CoV-2 Monoclonal antibody treatment is found to be useful in treatment of early Covid-19 as well as post exposure prophylaxis, preventing progression of the disease, hospitalizations and death among high risk patients with Covid-19.

STRUCTURE OF SARS-CoV-2 VIRUS:

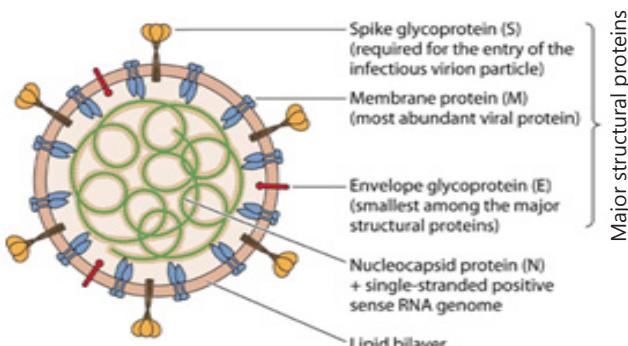


Figure-1: SARS-CoV 2 structure

The SARS CoV2 genome encodes four major structural proteins: (Figure-1)

- Spike (S)
- Envelope (E)
- Membrane (M)
- Nucleocapsid (N), as well as nonstructural and accessory proteins

The spike protein is further divided into two subunits, S1 and S2 that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and viral entry.

HISTORY OF MONOCLONAL ANTIBODIES:

From the time the first monoclonal antibody was generated in 1975 and the first monoclonal antibody fully licensed in 1986, there are approximately 30 monoclonal antibodies that have been approved for use in clinical practice with many more currently being tested in clinical trials. Monoclonal antibodies are monovalent antibodies which bind to the same epitope and are produced from a single B-lymphocyte clone. They were first generated in mice in 1975 using a hybridoma technique. The presently available monoclonal antibodies against SARS-CoV-2 virus IgG, is fully human and neutralizing in nature.

ANTIVIRAL ACTION OF MONOCLONAL ANTIBODIES:

Monoclonal antibodies directly interfere with the viral pathogenesis in following ways: (Figure-2)

- By neutralizing receptor binding domains, entry of the virus into host cell is prevented
- Antibodies cause antibody dependent cytotoxicity
- Antibodies cause antibody dependent enhanced phagocytosis.

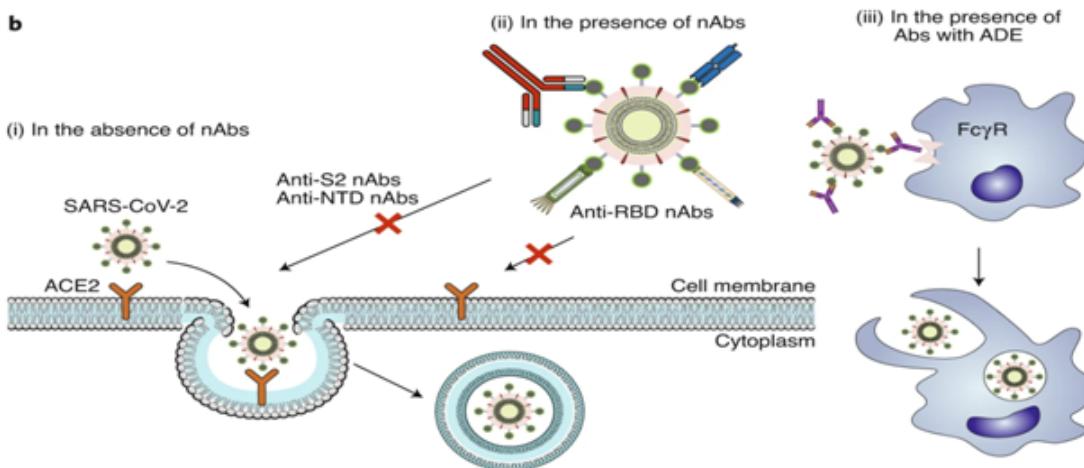


Figure-2 : Antiviral action of monoclonal antibodies

WHY TO USE ANTIBODY COCKTAIL?

The combination of two potent, virus-neutralizing antibodies that form the cocktail bind **non-competitively to the critical receptor binding domain** of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population.

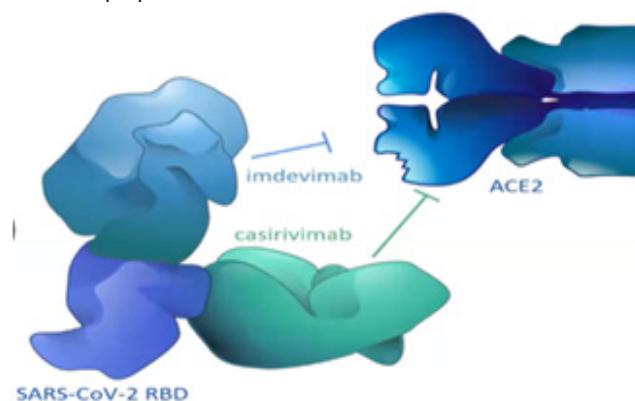


Figure-3: Antibody cocktail preventing SARS-CoV-2 from binding to ACE2 receptors

The FDA also updated the EUA for casirivimab plus imdevimab as post-exposure prophylaxis for certain individuals who are at high risk of acquiring SARS-CoV-2 infection and, if infected, are at high risk of progressing to serious illness. (Table 2)

WHO SHOULD BE CONSIDERED FOR MONOCLONAL ANTIBODY THERAPY?

In people > 12 years of age and weighing atleast 40 kgs, three criteria should be satisfied...

1. Positive COVID-19 diagnosis with < 10 days since symptom onset.
2. Mild to Moderate COVID disease (not hospitalised and not on oxygen support)
3. Presence of any risk factor for disease progression

Risk factors for Disease Progression

High-risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) >35
- Have chronic kidney disease

Table 1 : List Of Anti-sars-cov-2 Monoclonal Antibodies That Received Emergency Use Authorizations From Various Regulatory Authorities:

Drugs	Dosage	Route of Administration	US FDA	DCGI (India)	Other Countries
Casirivimab-Imdevimab (Regeneron)	600mg 600mg	IV/SC	Nov2020	May 2021	Several EU countries and gulf countries
Bamlanivimab Etesivimab(Eli Lilly)	700mg 1400mg	IV	Nov 2020	In process	Several EU countries and gulf countries
Sotrovimab (GSK & VIR Biotechnology)	500mg	IV	May 2021	?	Several EU countries and gulf countries
Regdanvimab (Celltrion)	40mg/kg	IV			EU countries

Table - 2 : CLINICAL EVIDENCE FOR THE USE OF MONOCLONAL ANTIBODIES:

Data from the following clinical studies cited is suggestive of 70-90% reduction of hospital admission and decrease in the emergency visits, ICU admission and mortality.

Date	Source	Trial Design / Patient	Reported Outcomes	Notes
Jan 2021	JAMA	RCT, n = 577	70% reduction in hospitalization for high-risk patients	Lilly trial (Phase 2)
Feb 2021	Website	Observational	50% decrease in hospitalizations, 40% decrease in emergency department visits	St. Luke's
Mar 2021	Lily	RCT, n = 769	87% relative reduction vs. placebo in hospitalizations / death	Lilly trial (Phase 3)
Mar 2021	Regenero	n RCT, n = 4,567	70% relative reduction vs. placebo in hospitalizations / death	Regen. trial (Phase 3)
Mar 2021	NEJM	Observational, n not listed	<ul style="list-style-type: none"> • 4.2% hospitalization rate for those treated with mAbs vs. 9-14.6% reported for untreated high-risk • Only 13% felt symptoms progressed after therapy 	Houston Methodist
Mar 2021	Medrxiv	Observational, n = 234 matched	<ul style="list-style-type: none"> • Patients receiving mAb had 69% lower odds of hospitalization or mortality, and 50% lower odds of hospitalization or ED visit without hospitalization • 6% hospitalization in treated vs. 16.2% untreated, 	UPMC
Apr 2021	Medrxiv	Observational, n = 270 treated, 328 untreated	1.9% of treated patients presented to E.D. / required hospitalization vs. 12% of untreated	ASPR

- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are >65 years of age

Age >55 years of age AND have

- cardiovascular disease, OR
- hypertension, OR
- chronic obstructive pulmonary disease/other chronic respiratory disease

Age 12 – 17 years of age AND have

- BMI >85th percentile for their age and gender based on CDC growth charts, OR
- sickle cell disease, OR

- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

CONTRAINdications TO ANTIBODY COCKTAIL :

- Hospitalised patients of COVID-19
- COVID 19 patients requiring oxygen to maintain saturations
- COPD patients on low flow oxygen and now

- increasing oxygen requirements
- Mechanically ventilated patients

ADVERSE EFFECTS & DRUG-DRUG INTERACTIONS:

- Hypersensitivity, including anaphylaxis and infusion related reactions, has been reported in patients who received anti SARS-CoV-2 monoclonal antibodies.
- Rash, diarrhoea, nausea, dizziness, pruritis have also been reported.
- Drug-drug interactions are unlikely between the authorized anti SARS-CoV-2 monoclonal antibodies and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors or inducers

USE OF ANTI SARS-CoV-2 MONOCLONAL ANTIBODIES IN SPECIFIC POPULATION:

- Pregnancy :** should only be used if the potential benefit outweighs the potential risk for the mother and the fetus.
- Lactation :** Should be considered along with the mother's clinical condition
- Pediatric use :** Not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg.

POTENTIAL RISKS OF MAB THERAPY:

- Immune Response Attenuation:** There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.
- Antiviral Resistance:** There is a potential risk of treatment failure due to the development of viral variants that are resistant to mAbs.
- Cross Resistance:** It is possible that resistance-associated variants to the casirivimab + imdevimab combination could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.
- Efficacy against mutants:**

The authorized SARS-CoV-2 monoclonal antibodies are effective against the presently prevalent viral strains as shown in the table 3 below.

PERSONS WHO PREVIOUSLY RECEIVED PASSIVE ANTIBODY THERAPY FOR COVID-19 AND COVID19 VACCINATION:

- Currently no data on safety or efficacy of COVID-19 vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment
- Vaccination should be deferred for at least 90 days to avoid interference of the treatment with vaccine-induced immune responses.
- Persons who received passive immunotherapy following FIRST dose of mRNA vaccine a gap of 90 days following receipt of immunotherapy is preferable before the second dose

SUMMARY:

Anti SARS-CoV-2 monoclonal antibodies when given within 72 hours of RT-PCR/Rapid antigen for SARS-CoV2 positive or within seven days of onset of symptoms, there is 70-90% reduction in the rate of progression to severe COVID-19, decrease the rate of hospitalization and mortality, early symptom relief , rapid reduction of viral load (Fewer mutations / No resistance to presently available vaccines) . Recently published data suggests these monoclonal antibodies can also be used as post exposure prophylaxis preventing progression of the disease in high risk populations. They are safe, well tolerated and can be used in the out-patient care. Anti SARS-CoV-2 Monoclonal antibodies are a game changer in management of COVID-19 .

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Table 3 : Efficacy of SARS-CoV-2 monoclonal antibodies against mutants

WHO Label	Pango Lineage	SARS Variant Class	Notable Mutations	Bamlanivimab Plus Etesevimab		Casirivimab Plus Imdevimab		Sotrovimab	
				In Vitro Susceptibility ^a	Activity ^b	In Vitro Susceptibility ^a	Activity ^b	In Vitro Susceptibility ^a	Activity ^b
Alpha	B.1.17	VoC	N501Y	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VoC	K417N, E484K, N501Y	Marked change	Unlikely to be active	No change ^c	Active	No change	Active
Gamma	P.1	VoC	K417T, E484K, N501Y	Marked change	Unlikely to be active	No change ^c	Active	No change	Active
Delta	B.1.617.2	VoC	L452R	Modest change ^d	Likely to be active	No change	Active	No change	Active
Epsilon	B.1.429/B.1.427	Vol	L452R	Modest change ^d	Likely to be active	No change	Active	No change	Active
Iota	B.1.526	Vol	E484K	Modest change ^d	Likely to be active	No change ^c	Active	No change	Active



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INTRODUCTION

The most common initial symptoms of coronavirus disease 2019 (Covid-19) are cough, fever, fatigue, headache, myalgias, and diarrhea. Severe illness usually begins approximately 1 week after the onset of symptoms. Dyspnea is the most common symptom of severe disease and is often accompanied by hypoxemia. Progressive respiratory failure develops in many patients with severe Covid-19 soon after the onset of dyspnea and hypoxemia. These patients commonly meet the criteria for the acute respiratory distress syndrome (ARDS), which is defined as the acute onset of bilateral infiltrates, severe hypoxemia, and lung edema that is not fully explained by cardiac failure or fluid overload. The majority of patients with severe Covid-19 have lymphopenia, and some have thromboembolic complications as well as disorders of the central or peripheral nervous system. Severe Covid-19 may also lead to acute cardiac, kidney, and liver injury, in addition to cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock. These organ failures may be associated with clinical and laboratory signs of inflammation, including high fevers, thrombocytopenia, hyperferritinemia, and elevations in C-reactive protein and interleukin-6.

Patients with severe disease typically require supplemental oxygen and should be monitored closely for worsening respiratory status because some patients may progress to acute respiratory distress syndrome (ARDS).

GOAL OF OXYGENATION

The optimal oxygen saturation (SpO_2) in adults with COVID-19 is uncertain. However, a target SpO_2 of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an $\text{SpO}_2 < 92\%$ or $> 96\%$ may be harmful. The ICU-ROX trial and the LOCO trial conducted in non covid ARDS patients found

no benefit from conservative oxygen therapy and liberal oxygen therapy. However hyperoxia should be avoided.

If a higher SpO_2 is achieved during initial resuscitation and stabilization, supplemental oxygen should be weaned as soon as is safe to avoid prolonged hyperoxia. Individualization of the goal is important, as some patients may warrant a lower target (eg, patients with a concomitant acute hypercapnic respiratory failure from chronic obstructive pulmonary disease [COPD]) and others may warrant a higher target (eg, pregnancy).

PATIENTS WITH MINIMAL OXYGEN NEEDS

For patients with hypoxic respiratory failure due to COVID-19, supplemental oxygenation with a low-flow system (ie, up to 6 L/minute) via nasal cannulae is appropriate as an initial strategy. The degree of viral aerosolization at low-flow rates is unknown but likely minimal.

As patients progress, higher amounts of oxygen are needed. Higher flows of oxygen (eg, up to 10 L/minute, sometimes 15 L/min) may be administered through a low-flow system (eg, simple face mask, venturi facemask, or nonrebreather mask) in patients with increased oxygen requirement.

When higher fractions of oxygen greater than 6 L/minute are required, many clinicians, move directly to delivering high-flow oxygen via nasal cannulae (HFNC) through a high-flow system. Rationale for moving directly to HFNC in such cases is one of convenience, so that high fractions of oxygen can be easily and comfortably provided and titrated.

PATIENTS WITH REQUIREMENTS FOR ADVANCED RESPIRATORY SUPPORT

Once oxygen requirements start to increase over 6 to 15 L/min or breathing becomes laboured, options

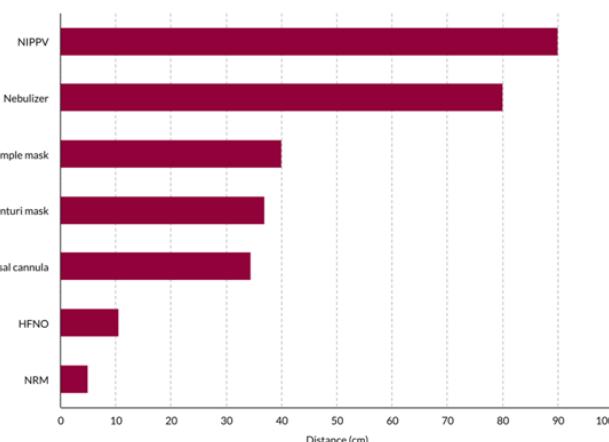
are high-flow oxygen via nasal cannulae (HFNC), oxygen delivered via a noninvasive ventilation (NIV) device, or invasive mechanical ventilation. Among these options, an initial trial of HFNC is recommended unless there is a separate indication for a different modality (eg, concomitant acute hypercapnia requiring bilevel positive airway pressure).

Noninvasive modalities

Severe COVID-19 causes significant numbers of patients to develop respiratory symptoms that require increasing interventions. Initially, the treatment for severe respiratory failure included early intubation and invasive ventilation, as this was deemed preferable to be more effective than Non-Invasive Ventilation (NIV). However, emerging evidence has shown that NIV may have a more significant and positive role than initially thought. NIV includes Continuous Positive Airway Pressure (CPAP) and Bi-Level Positive Airway Pressure (BiPAP). CPAP is the method of choice with the use of BiPAP for those with complex respiratory conditions who contract COVID-19. The use of High Flow Nasal Oxygen (HFNO) has increased for treatment in covid 19 with hypoxic respiratory failure. Current thinking suggests that NIV and HFNO may be an appropriate bridging adjunct in the early part of the disease progress and may prevent the need for intubation or invasive ventilation.

HFNC(high flow nasal cannulae)

Comparison of aerosol dispersion differences, using various treatment modalities.



HFNC, although initially controversial due to its aerosolizing potential, it was found to be safe in further studies, with a bio-aerosol dispersion not significantly different from regular nasal prongs.

Airborne precautions among the treating staff should be maintained and the patient should be placed in a negative pressure room if available.

High-flow oxygen therapy through a nasal cannula is a technique whereby heated and humidified oxygen is delivered to the nose at high flow rates. These high flow rates generate low levels of positive pressure in the upper airways, and the fraction of inspired oxygen (FIO_2) can be adjusted by changing the fraction of oxygen in the driving gas. The high flow rates may also decrease physiological dead space by flushing expired carbon dioxide from the upper airway, a process that potentially explains the observed decrease in the work of breathing. In patients with acute respiratory failure of various origins, high-flow oxygen has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask.

HFNO is sometimes used for patients with increased respiratory effort e.g. tachypnoea, shortness of breath, increased work of breathing in the presence of hypoxia, evidence of type 1 respiratory failure and desaturation despite increasing oxygen requirements. However, contra-indications include severe respiratory distress, severe cardiovascular instability, unconscious patients, upper airway obstruction, basal skull fractures, epistaxis and an impaired ability to cough or clear secretions. It must be noted that HFNO dries the lining of the respiratory system. Therefore, a humidification water chamber and fluid bag is used and must be checked regularly to maintain water levels and the humidification circuit temperature of 37 degree C.

HFNO tends to be initially commenced at a flow rate of 60litres/min and oxygen to achieve the target saturations (SpO_2). Patients must be continuously monitored and vital signs recorded to determine if there is any improvement, when the therapy can then be titrated. If there is no initial improvement, oxygen levels should be increased until target saturations are achieved. However, if the oxygen is >50% the patient should be urgently re-assessed as intubation may be appropriate. It must be noted that in COVID-19, the intubation team will require enhanced personal protective equipment (PPE), which may extend the time before intervention is possible. When clinically indicated, oxygen should

be weaned first before the flow. When weaning the flow, this should be decreased at 5 litres at time, or as tolerated by the patient.

Failure of HFNC may cause delayed intubation and increased mortality in patients with acute respiratory failure. Failure of HFNC is determined by ROX index. ROX index is defined as the ratio of pulse oximetry/fraction of inspired oxygen ($\text{SpO}_2/\text{FiO}_2$) to respiratory rate (RR).

Assess ROX index at regular intervals. A ROX index of >4.88 indicates success of HFNC and ROX index of <2.85 indicates failure and consider for intubation in these subset of patients. A value in between patients should be monitored closely.

ROX	
≥ 4.88	Little risk of intubation
3.85-4.87	close monitoring due to increased risk of intubation
2.85-3.84	Monitoring in the ICU if possible. Highly increased risk of intubation
<2.85	Consider intubation

NIV(Non invasive ventilation)

NIV can be initiated in few subset of population with covid 19. NIV is reasonable in patients with indications that have proven efficacy in the absence of COVID-19. This includes patients with acute hypercapnic respiratory failure from an acute exacerbation of chronic obstructive pulmonary disease, patients with acute cardiogenic pulmonary edema, and patients with underlying sleep-disordered breathing (eg, obstructive sleep apnea or obesity hypoventilation).

NIV is not sufficient to manage type 1 respiratory failure in all patients presenting with severe COVID-19. For some patients, while NIV may temporarily improve oxygenation and work of breathing, it does not change natural disease progression and is not a replacement for intubation and invasive ventilation. However, there is emerging evidence that there is a place for NIV in the care of patients post

extubation. Review of early data suggests more than 50% of patients have required re-intubation and it is now thought that NIV support may bridge support for this group of patients where fatigue remains a significant symptom, and help in breathing is needed to aid recovery.

Steps to follow when using NIV to treat patients with COVID-19

1. Ensure that you are able to get a negative pressure room. If none are available, obtain a single occupancy room and ensure the door is closed at all times.
2. Choose the best interface for the patient's tolerance. When available, consider a helmet or full-face mask interface to minimize particle dispersion. Ensure a good seal, and make sure the mask does not have an anti-asphyxiation valve or cord.
3. Use dual limb circuitry with a filter on the expiratory limb of a critical care ventilator. This may decrease dispersion compared with single limb circuitry portable devices.
4. Start with continuous positive airway pressure (CPAP) using the lowest effective pressures, between 5 and 8 cmH₂O. Early reports suggest most patients with COVID-19 are not hypercapnic, so bilevel positive airway pressure (BPAP) may result in increased inspiratory pressures without any added benefit.
5. Re-evaluate patients within the first few hours of therapy. If patients are not responding, consider intubation and mechanical ventilation.

There are two types of NIV: CPAP and BiPAP (Bi-Level Positive Airway Pressure)

Continuous positive airway pressure (CPAP)

CPAP delivers a constant flow of oxygen at a prescribed pressure, measured in cmH₂O, which remains constant during inspiration and expiration. Intrinsic positive end expiratory pressure is the residual volume preventing collapse of the alveoli normally measuring around 2.5 cmH₂O. CPAP is

usually commenced at a higher level than normal intrinsic pressure around 5cmH₂O. For most patients with type 1 respiratory failure, it is secondary to conditions which either collapse the alveolar or widen the gap between the alveolar and the blood vessels that surround them thereby reducing gaseous exchange. The application of Positive End Expiratory Pressure (PEEP) assists in maintaining the patient's airway pressure prevents alveolar collapse, in turn increasing lung volumes and distends them to reduce the distance between the alveolar and the blood vessels to improve gaseous exchange. In severe COVID-19, initial CPAP settings have been suggested 10 cmH₂O and 60% oxygen.

For CPAP to be effective, a sealed system is required, through application of a tight-fitting mask or a hood. Both methods for establishing a sealed system have benefits and disadvantages. With a face mask, the tight fit means patients may experience pressure damage to the nasal bridge. Newer types of facemask are available with high-volume low-pressure seals which reduce the pressure needed to create the seal when applied correctly. An ill-fitting mask leads to significant leaks, resulting in poor inflation of the lungs, with dry oxygen/air leaking round a mask likely to lead to irritation, abrasions, and oedema of the cornea and conjunctiva. The second method, a CPAP hood, requires the patient's head to be fully enclosed with a secure seal around the neck and the hood can be supported by straps under the armpits. While such hoods reduce the risk of facial pressure sores, when straps are used, they can cause discomfort, pain and potentially with prolonged use, pressure sores. It also has to be noted that for many patients the noise generated from the high flow required impedes communication with Healthcare staff and for some, causes claustrophobia which is counterproductive in terms of recovery. A potential complication is that gasping breathing, and reduced compliance of the lungs can lead to air being swallowed, which if not addressed will lead to gastric distension and vomiting, with a risk of aspiration of gastric contents. As with COVID-19 type diseases, patient's lungs are less compliant, the risk of developing barotrauma and pneumothorax must be recognised and observations regularly taken and in the light of

the rapid deterioration that occurs with COVID-19 urgent, early intervention is essential. If positive pressure ventilation is continued where there is an undrained pneumothorax, it can lead to a tension pneumothorax and potentially cause cardiac arrest. As cited above, due to the need for a tight-fitting mask, regular assessment of the patient's pressure areas on the face must be taken, and protective dressings applied if necessary. Note where there is a naso-gastric tube in place, dressing is more likely to be needed. For both CPAP and BiPAP to be effective, the patient is required to wear the mask for extended periods of time, to recruit and maintain alveolar distension with the pressure settings. It has to be noted that it is less likely to be effective in patients who have poor tolerance to the pressures and have a productive cough as secretions will require frequent removal of the mask for suctioning of oral or nasopharyngeal secretions.

Bilevel positive airway pressure (BiPAP)

NIV BiPAP is commonly used in the care of patients with chronic respiratory disease, such as COPD, so it may be useful in COVID19 for patients who have co-morbidities such as COPD plus COVID-19. In COVID-19, BiPAP may have a clinical use to improve the work of breathing. However, it carries a risk that inappropriate settings may allow the patient to take an excessively large tidal volume causing baro and volutrauma. This resembles CPAP but provides some additional support. Prior to commencing BiPAP, the patient must be assessed for a pneumothorax, ideally by a chest X-Ray or ultrasound. Due to the need for PPE chest auscultation for COVID-19 patients, is not recommended as it increases the risk of transmission to the Healthcare professional.

Inspiratory Positive Airway Pressure (IPAP) settings can be varied to achieve adequate tidal volumes, by allowing patients to breath to a pre-set inspiratory pressure. To achieve adequate tidal volumes, the IPAP can range from 12 to 35 cmH₂O. Expiratory Positive Airway Pressure (EPAP) works on the same principles as PEEP in CPAP devices, preventing alveolar collapse on expiration which is maintained above atmospheric pressure. To overcome the difficulty of breathing on a ventilator (including valves) and increase of dead space from the ventilator tubing is achieved by pressure

support. Pressure support is calculated by minus IPAP from EPAP, and it is recommended that there should be a difference of at least 8cmH₂O, with supplementary oxygen provided, if needed, to achieve oxygenation. Some BiPAP ventilators offer a 'ramp' setting, also termed 'rise time', which allows the pressure to be slowly increased over the first few minutes of ventilation until the required pressure is reached. This prevents barotrauma and is considered less distressing for the patient when treatment is commenced. Using this approach, a 25% rise time will take up 25% of the total inspiratory time before the peak pressure is reached. Given BiPAP may be used where there are multiple comorbidities, decisions regarding escalation in treatment must be agreed prior to the treatment. BiPAP may be used as a trial, with a view to intubation if this fails. The treatment escalation plan should have been discussed with the patient and relatives prior to commencing treatment (if it is not life threatening). Patients and families need to be aware of when BiPAP is the ceiling of treatment and should have discussed palliation and end of life care.

Nursing considerations for patients requiring NIV and HFNO

Patients requiring NIV or HFNO must be nursed in specialist settings, with higher nurse to patient ratios to support continual observation. Nurses redeployed or working outside of intensive care units must be given adequate training to care for patients requiring respiratory support using different sets of equipment used. In addition, as HFNO and CPAP require significant demands of oxygen, hospital oxygen supplies may become depleted leading to critical failures in availability not just locally but regionally and nationally.

Both NIV and HFNO are classed as an aerosol generating procedure (AGP) and increase the risk of viral transmission. When disconnecting patients from NIV or HFNO, all equipment should be placed into the standby mode to minimize the spread of the virus in the atmosphere. To reduce the risk of aerosolization, when using HFNO, the patient should wear a surgical mask to reduce particle dispersion, and care must be used with viral filters and all secure connections. Healthcare professional must use enhanced PPE for all procedures, with, where

possible, patients cohorted within a negative pressure environment.

Patient assessment and observations must include continuous pulse oximetry, hourly vital and neurological signs, together with an early warning scoring (if used). Added observations include checking for respiratory deterioration, such as increased work of breathing or worsening breathing pattern, use of accessory muscles and mouth breathing, tachypnoea and bradypnoea. Decreasing saturations and/or increasing oxygen requirements to maintain oxygen saturations must be recorded and reported. Arterial blood gases (ABG) should be recorded as clinically indicated, but at the least, within 1 hour of starting treatment and repeated within four and 12 hours. Patients at risk of further deterioration may benefit from an arterial line which allows for continuous blood pressure monitoring and for ABGs to be taken as clinically indicated.

NIV causes raised intrathoracic pressure, which for patients who are haemodynamically unstable, may compromise cardiovascular stability through reducing venous return. There may also be challenges with maintaining an appropriate fluid balance. As patients with severe COVID-19 usually present with history of fever and increased shortness of breath, they may be intravascularly dehydrated. Insensible losses, accrued over the proceeding days prior to admission to hospital, associated with fever and high respiratory rates will, therefore, need to be considered and factored in when planning fluid balance. This is crucial because there is a 25% incidence of COVID-19 patients admitted to critical care units develop acute kidney injuries (AKI).

Periods off NIV should be of short duration, to prevent desaturation, but as patients are conscious, they need time limited breaks to eat and drink, with regular mouth care to prevent problems from dry and sore mouth. Nutritional supplements may be required if there is poor oral dietary intake and nasogastric (NG) feeding may need to be considered. However as conscious proning is being increasing used, NG feeds need to be stopped prior to position changes and gastric aspirates monitored. In addition, care must be taken to avoid patients lying supine with continuous enteral feeds running, as this increases the risk of pulmonary aspiration.

Awake prone positioning in COVID-19

In the absence of effective targeted therapies for COVID-19, optimisation of supportive care is essential. Lung injury with features of acute respiratory distress syndrome (ARDS) appears to be the principal characteristic of severe acute respiratory syndrome coronavirus 2 infection. Recent guidance by the UK Intensive Care Society (ICS) advocates awake prone positioning to become standard of care for suspected or confirmed COVID-19, in patients requiring an $\text{FiO}_2 \geq 28\%$. These recommendations are extrapolated from physiological principles and clinical evidence obtained in a distinct study population—patients with severe ARDS undergoing invasive mechanical ventilation (IMV).

The physiological rationale behind prone positioning in typical ARDS is to reduce ventilation/perfusion mismatching, hypoxaemia and shunting. Prone positioning decreases the pleural pressure gradient between dependent and nondependent lung regions as a result of gravitational effects and conformational shape matching of the lung to the chest cavity. This is believed to generate more homogenous lung aeration and strain distribution, thus enhancing recruitment of dorsal lung units. Prone positioning does not appear to alter regional distribution of pulmonary blood flow, with perfusion predominating towards dorsal lung aspects due to nongravitational factors. With improvements in ventilatory homogeneity and relatively constant perfusion patterns, a subsequent reduction in shunting is observed. The use of positive end-expiratory pressure via non-invasive ventilation (NIV) or CPAP in the management of ARDS is beneficial by preventing alveolar de-recruitment but may also result in overdistension of previously well-ventilated alveoli. Similarly, spontaneously breathing patients in acute hypoxaemic respiratory failure can generate high respiratory drives and forceful inspiratory efforts that lead to lung injury reminiscent of ventilator induced lung injury. Prone positioning in these patients and in combination with NIV/CPAP may help to mitigate this detrimental effect in part by reducing regional hyperinflation.

Prone positioning is an established evidence-based practice in patients with typical ARDS undergoing IMV, but limited evidence exists in non-ventilated awake patients. In a multicentre, randomised controlled trial of patients with severe ARDS receiving IMV, prone positioning halved 28-day mortality rates (16% vs 32.8%, $p < 0.001$) with no additional complications.¹⁰ Meta-analyses suggest that early prone positioning for 12–16 hours/day combined with low tidal volume IMV reduces mortality in severe hypoxic respiratory failure.

Presently, no published trials investigate the effectiveness of prone positioning in awake patients with typical ARDS. Evidence in awake prone positioning is limited to case series and small observational studies with heterogeneous approaches to non-invasive respiratory support. These reports demonstrated short-term improvements in oxygen requirements (PaO_2) and demand (FiO_2) with no harm to patients. Valter et al applied prone positioning to four patients with indications for IMV and found rapid improvements in PaO_2 —all patients avoided IMV and tolerated prone positioning well. In an observational study of 15 patients receiving non-invasive respiratory support for acute hypoxaemic respiratory failure, repeated prone positioning led to transient but substantial improvements in oxygenation. In a prospective observational study of 20 patients receiving non-invasive ventilation for moderate-to-severe ARDS, $\text{PaO}_2 / \text{FiO}_2$ ratio increased by 25–35 mm Hg following awake prone positioning; but 78% of participants with severe ARDS eventually required IMV, and therefore awake prone positioning should not delay the use of IMV when indicated.

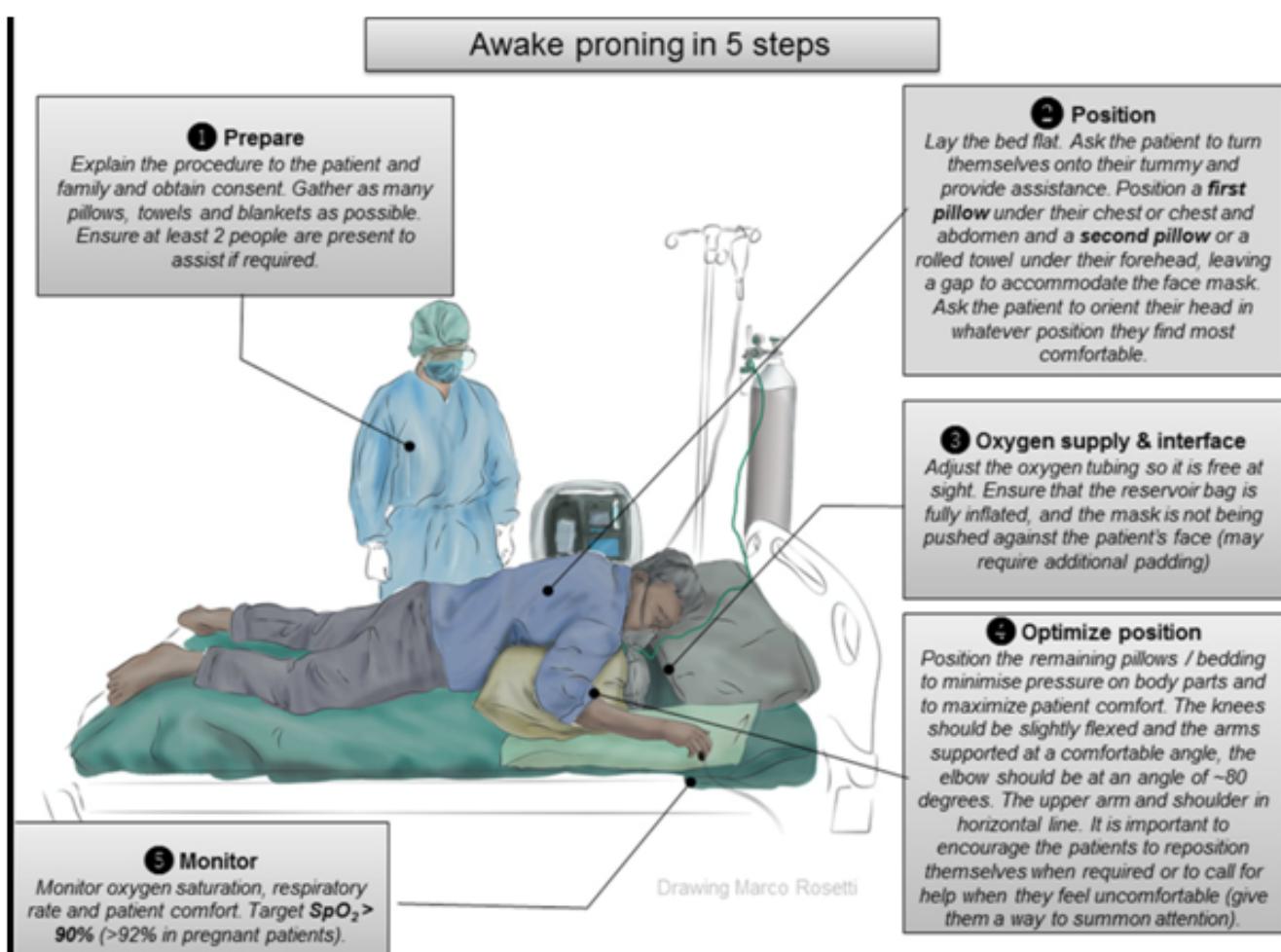
In early phases of COVID-19 pneumonitis, lung compliance is proposed to be high, recruitability minimal and hypoxaemia predominantly driven by impaired regulation of pulmonary perfusion patterns. Awake prone positioning here could temporarily improve ventilation/perfusion mismatch, but sustained benefits in highly compliant lungs are unlikely. With disease progression, COVID-19 pneumonitis is thought to gradually start behaving like typical ARDS, demonstrating lower compliance and higher

recruitability with a more favourable long-term response to prone positioning.

Furthermore, the minimum duration requirements for maintaining the prone position in awake patients to engender clinically meaningful benefits remain undefined. Durations comparable to those necessary for patients undergoing IMV (12–16 hours/day) may be difficult to achieve. For instance, the longest duration of prone positioning achieved in observational studies of awake patients was 8 hours. Improved lung secretion drainage under gravitational forces and increased coughing following prone positioning may contribute to viral contamination of the patient environment, necessitating the use of adequate personal

protective equipment during patient contact.

In summary, awake prone positioning appears to be safe and may slow the respiratory deterioration in select patients with COVID-19, who require oxygen supplementation or NIV/CPAP. This in turn may reduce demand for IMV. In resource-limited settings, this simple, low-cost intervention may serve to raise the ceiling of care for patients that might otherwise have no further option. However, a blanket policy for awake prone positioning in COVID19, may overstretch personnel without achieving clinically tangible benefits. This may be particularly relevant outside of critical care settings, where staff is likely to be inexperienced and untrained in the adoption of prone positioning.



INVASIVE VENTILATION

The appropriate triggers for tracheal intubation include altered mental status, hemodynamic instability and failure to maintain SpO₂ > 90% with non-invasive respiratory interventions.

The decision for tracheal intubation in patients receiving non-invasive respiratory support is challenging, requiring a fine balance between early intubation and risks of invasive mechanical ventilation versus the adverse effects of delaying intubation. The impact of early versus delayed tracheal intubation has not been compared in patients with covid ARDS(CARDS). The decision for tracheal intubation in COVID-19 patients may be best determined using a combination of factors that include clinical acumen, oxygen saturation, dyspnoea and respiratory rate . Experts recommended the use of clinical criteria to be preferred over the use of arterial blood gas or imaging findings to determine the need for tracheal intubation.

Possible Clinical Indications for Endotracheal Intubation

- Impending airway obstruction
- Signs of unsustainable work of breathing
- Refractory hypoxemia
- Hypercapnia or acidemia
- Encephalopathy or inadequate airway protection

Additional Considerations

- Does illness trajectory predict deterioration?
- Are difficulties in endotracheal intubation anticipated?
- Is there hemodynamic instability?
- Will intubating now improve the safety of a planned procedure or transportation?
- Will intubating now improve infection control and staff safety?

ARDS is defined as a form of inflammatory pulmonary edema of non-cardiogenic etiology, with a reduction in the areas of normoventilated lung and consequent reduction in respiratory compliance and shunt effect. The Berlin definition proposed categories of ARDS based on degree of hypoxemia:

mild ($\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$), moderate ($\text{PaO}_2/\text{FiO}_2 < 200 \text{ mm Hg}$), and severe ($\text{PaO}_2/\text{FiO}_2 < 100 \text{ mm Hg}$): radiographic severity, respiratory system compliance (<40 mL/cm H₂O), positive end-expiratory pressure (>10 cm H₂O), and corrected expired volume per minute (>10 L/min).

To manage these patients, maneuvers that lead to recruitment of collapsed areas are usually applied, such as increased positive end-expiratory pressure (PEEP), alveolar recruitment maneuvers, and prone position, leading to a reduction in elastance and increased compliance . Prone positioning presents the potential benefit of a relieve of severe hypoxemia due to reduction of overinflated lung areas, promoting alveolar recruitment and decreasing ventilation/perfusion mismatch. This intervention might be considered in patients with $\text{PO}_2/\text{FiO}_2 < 150$, in the absence of contraindications. The main objective of mechanical ventilation in these patients is to maintain a lung-protective strategy for all patients with ARDS, defined as targeting a tidal volume of 4 to 8 mL/kg predicted body weight (PBW) and a plateau pressure of less than 30 cmH₂O.

A group of experts hypothesize that in COVID, there may be two phenotypes of ARDS . Patients often exhibit normal compliance even in the presence of severe hypoxemia, with normal or even increased minute ventilation, and more than half of these patients do not appear dyspneic. Radiologically, such patients have ground-glass tomographic lesions indicative of interstitial and nonalveolar edema, and these infiltrates are relatively limited in extent at this stage. These patients are called "type L" ("low elastance"), with additional main characteristics of high compliance, low response to PEEP, and low lung weight estimated by chest computed tomography (CT) . Patients may evolve with progressive clinical improvement or, whether due to individual predisposing factors or inadequate management, evolve with a more severe form closer to the classic ARDS. This is named as "type H" (from "high elastance"), showing also low compliance, high response to PEEP, and high lung weight estimated on chest CT . It should be highlighted that this division is conceptual, to facilitate the understanding of the respiratory condition, with types "H" and "L"

representing the ends of a spectrum that frequently overlap.

Mechanical ventilation strategy according to patient phenotypes ("type L" or "type H")

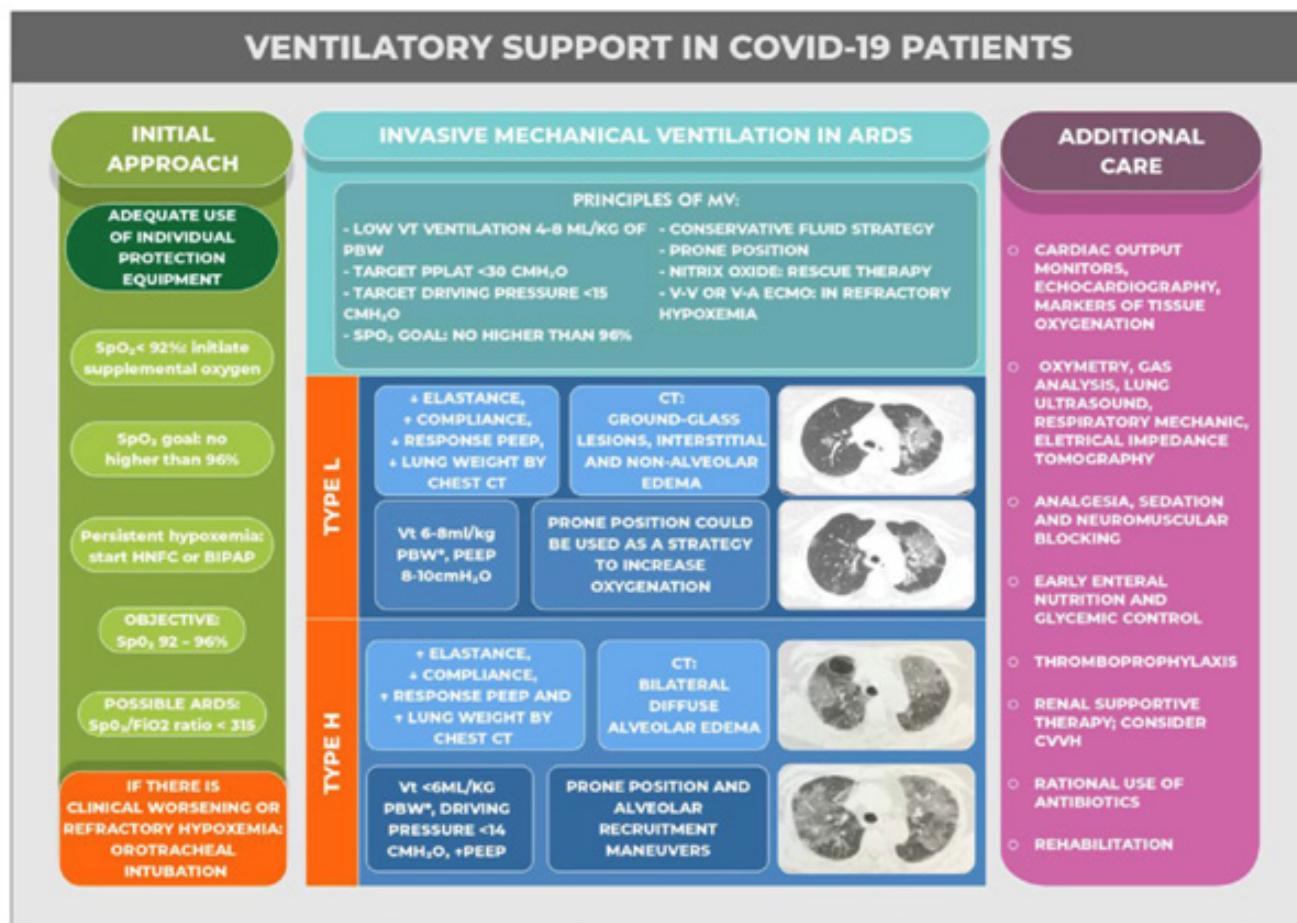
In severe cases of respiratory failure, as frequently seen in SARS-CoV-2-related ARDS, severe hypoxemia can lead to a persistent increase in respiratory effort, with consequent self-induced lung injury (P-SILI). In addition, other factors such as fluid overload or SARS-CoV-2-induced myocardial injury may also play important roles in worsening of the condition through pulmonary congestion. Thus, a mechanical ventilation strategy must take into account the multiple mechanisms of lung injury and the different presentations of the disease—conventional form of ventilation in ARDS will not always be the most appropriate, as described below

- **Type L:** it is suggested to ventilate "type L" patients, typically patients with good lung compliance, higher tidal volumes (VT) (around 7–8 mL/kg of ideal body weight). Higher VT helps to avoid reabsorption atelectasis and hypercapnia due to limited VT-induced hypoventilation. The rationale behind this strategy is as follows: the initial feature of these patients is the vasoregulation defect in the pulmonary capillaries—the reflex vasoconstriction that normally occurs in response to hypoxemia is not found in these patients due to endothelial changes and microthrombosis. Elevation of FiO₂ may be sufficient in most patients not experiencing excessive respiratory effort, with maintenance of NIV with BIPAP or HFNC leading to slow and progressive improvement of hypoxemia and reversal of ARDS. However, if the inflammatory condition progresses, or if the patient's ventilatory effort is excessive, secondary pulmonary tissue stress may lead to P-SILI, with severe deterioration of lung function. At this point, intubation with adequate sedation/paralysis can interrupt the vicious cycle. These patients should be

ventilated with lower PEEP (between 8 and 10 cmH₂O) to avoid redirection of blood flow away from the aerated pulmonary capillaries, which would increase the shunt effect. As capillary hypoperfusion can also suffer a gravity-dependent effect, the prone position could be used as a strategy to minimize it and increase oxygenation.

- **Type H:** with disease progression and worsening of inflammatory edema, the patient may progress to "type H". The pathophysiology of this progression is probably the result of a combination of factors: in addition to self-induced lesion (P-SILI), the viral lesion itself leads to uncontrolled inflammation and edema, with local and generalized thrombogenesis, intense release of cytokines, and right ventricular overload. The resulting pulmonary edema is close to classic ARDS presentation, with collapsed alveoli and extensive normoperfused and hypoaeerated areas. In these more advanced cases, a mechanical ventilation strategy should be more traditional: elevated PEEP, VT < 6 mL/kg, driving pressure < 14 cmH₂O, prone position, and alveolar recruitment maneuvers in refractory cases.

As previously stated, categorization in two different profiles facilitates clinical management by indicating the need for different ventilatory approaches. However, due to the frequent overlap of the two types, individualization of ventilatory management is essential. In either case, patients with COVID-19 who undergo mechanical ventilation have an average recovery time of 1–3 weeks. The progress toward improvement is characteristically slow; therefore, prolonged sedation is often unavoidable. In most severe cases of ARDS and also in cases of non-protective ventilation or in the occurrence of asynchrony, neuromuscular blockage is useful, and complications such as polyneuropathy of the critically ill patient are usually diagnosed.



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Introduction

RECOVERY trial a large well conducted RCT which showed that steroids reduce mortality significantly in corona virus disease 2019 (Covid-19) patients who require supplemental oxygen and who require invasive mechanical ventilation. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%). Numerous reports from across the world indicate that the mortality is 30-50% in patients who are mechanically ventilated in spite of using corticosteroids. There is an unmet need to further reduce the mortality in severe Covid-19 patients.

Rationale for use of Baricitinib in COVID-19

Scientific data shows that morbidity and mortality is due in part to a dysregulated inflammatory response which in turn is the main cause for Acute respiratory distress syndrome (ARDS) and death. Drugs which can mitigate the dysregulated inflammation may lead to improved outcomes. JAK/STAT pathway (Janus associated kinase and signal transducer and activation of transcription) play an important role in signal transduction and intracellular signalling of various cytokines involved in cytokine storm.

Mechanism of action of Baricitinib

Baricitinib, a small molecule, oral selective Janus-kinase inhibitor 1 and 2 (JAK inhibitor) has been used in various immunological conditions and approved in 65 countries for the treatment of moderate to severe Rheumatoid Arthritis. Artificial intelligence algorithms have predicted that Baricitinib could be a potential therapeutic option in management of ARDS and multiple organ damage secondary to severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by interrupting the cytokine signaling pathways. When cytokines or growth factors bind to their respective receptors on surface of cell membrane, the signal is transmitted to the nucleus via activation of JAK pathway which in turn leads to phosphorylation of STATS (Signal transducers and activation of transcription). The STATS translocate to nucleus and bind to DNA to initiate transcription of various genes involved in causing hyperinflammation.

Similar to all JAK-STAT inhibitors Baricitinib inhibits intracellular signaling pathway of various cytokines known to be elevated in severe COVID-19 including interleukin-6, interleukin-10, interferon- α , and granulocyte-macrophage colony stimulating factor. Baricitinib also inhibits viral cellular entry and infectivity by inhibiting host associated AP2-associated protein kinase (AAK) required for

viral cell entry. Inhibition of AAK leads to inhibition of clathrin mediated endocytosis. Baricitinib also down regulates the expression of ACE-2 receptor required for the cell entry.

Evidence for use of Baricitinib in COVID-19

Few smaller clinical trials on patients with Covid-19, have proved that baricitinib treatment was associated with both an improvement in oxygenation and a reduction in select inflammatory markers.

One among those studies by Titanji BK, Farley MM, Mehta A, et al. suggested a potential role for baricitinib in the treatment of COVID-19 based on artificial intelligence algorithms. They hypothesized that Baricitinib, a JAK1/2 inhibitor, could directly mitigate the inflammatory response triggered by SARS-CoV-2 infection. In addition, Baricitinib was identified as a numb-associated kinase (NAK) inhibitor with high-affinity for AP2- associated protein kinase 1 (AAK1). AAK1 was previously described as a crucial regulator of clathrin-mediated endocytosis of coronavirus and other viruses. In light of this, baricitinib may have direct antiviral effects by preventing virus entry into target cells. This mechanism could be complementary to potential anti-inflammatory benefits in the setting of the cytokine storm associated with severe COVID-19.

Other smaller study by Cantini F et al. Showed that the 2-week case fatality rate was significantly lower in the baricitinib-arm compared with controls. Discharge rate was significantly higher in the baricitinib-arm at week 1 and at week 2. Except ageusia/anosmia, all clinical, laboratory and respiratory functions significantly improved at week 1,

SpO₂ significantly improved at week 2 PaO₂/ FiO₂ significantly improved at weeks 1 and 2 compared with baseline. CRP and IL-6 levels significantly decreased in the baricitinib-arm. Interestingly, a significant reduction of positive nasopharyngeal swabs was observed in the baricitinib-arm at discharge, with only 12.5% positive-swabs compared to 40% in the control-group, confirming the anti-inflammatory and anti-viral effects of the baricitinib.

A study by Rodriguez-Garcia JL, Sanchez-Nievas G, et, al. compared the use of baricitinib along with corticosteroids which showed a greater improvement in SpO₂/FiO₂ from hospitalization to discharge in the BCT-CS (corticosteroids and baricitinib) vs CS (corticosteroids) group proving a conclusion of combination of baricitinib with corticosteroids was associated with greater improvement in pulmonary function when compared with corticosteroids alone. The short-term administration of the drug compared to the long-term treatment in rheumatoid arthritis, may probably explain the absence of serious AEs. In conclusion, baricitinib is a promising and safe therapy in patients with moderate COVID-19 pneumonia.

The Adaptive Covid-19 Treatment Trial -2 (ACTT-2)

The results of this randomized, double-blind, placebo-controlled trial show that combination treatment with the anti-inflammatory drug baricitinib and the antiviral drug remdesivir was safe and superior to remdesivir alone for the treatment of hospitalized patients with Covid-19 pneumonia. The beneficial effects of the combination treatment were seen both in

the primary outcome, with a 1-day shorter time to recovery, and in the key secondary outcome, with a greater improvement in clinical status as assessed on the ordinal scale. The observed benefit of combination treatment was most evident in patients with a baseline ordinal score of 5 (supplemental oxygen) or 6 (high-flow oxygen or non-invasive ventilation) with combination treatment than with placebo. Patients with a baseline ordinal score of 6 who received combination treatment were twice as likely as those in the control group to have improved clinical status at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6). The faster recovery in patients who received baricitinib plus remdesivir suggests that the combination treatment may have an effect in lowering the hospital-associated risk of nosocomial infections, thrombosis. In addition, the combination treatment showed clinical benefits directly relevant to patient care, such as a difference of "17.4 percentage points in new use of oxygen (22.9% vs. 40.3%) and a difference of "5.2 percentage points in new use of mechanical ventilation or ECMO (10.0% vs. 15.2%). In fact, the odds of progression to death or invasive ventilation were 31% lower in the combination group than in the control group (hazard ratio, 0.69; 95% CI, 0.50 to 0.95), and patients in the combination group had 11 fewer days receiving new mechanical ventilation than those in the control group. Patients receiving baricitinib plus remdesivir also had a significantly lower incidence of adverse events. The consistently lower incidence of adverse events with baricitinib may be related to its action in reducing inflammatory-mediated lung injury and improving lymphocyte counts, its antiviral properties, or its associated shorter recovery

time and faster clinical improvement, all of which could have reduced the risk of nosocomial infection. In summary, results and the characteristics of baricitinib, includes the fact that it is an oral drug with few drug-drug interactions and a good safety profile, lend itself to be used in low-to middle-income countries.

Dose

Baricitinib is given at a dose of

- 4mg orally (once daily) for 14 days or until hospital discharge whichever is earlier
- 2mg orally (once daily) for 14 days or until hospital discharge (2yrs to less than 9yrs paediatrics)

Note: - Evaluation of baseline eGFR, Liver enzymes and complete blood count to determine treatment suitability and dose. Therapy is not recommended in patients who are on dialysis, have end stage renal disease (ESRD, eGFR of less than 15mL/min) or who have active tuberculosis).

- Do not initiate treatment in patients with absolute lymphocyte count less than 500cells/mm, or who have Hb value less than 8g/dl

Renal modification

- **eGFR-** 30 to less than 60mL/min/1.73m² in covid-19 reduce dosage to 2mg once daily in adults and 1mg once daily in paediatrics
- **eGFR-** 15 to less than 30 ml/min/1.73m² in covid-19 Reduce the dose to 1mg once daily in adults and not recommended in paediatric patients

- **eGFR-** less than 15 mL/min/1.73m² in covid-19- not recommended
- Dialysis in Covid-19 not recommended

INDICATION FOR BARICITINIB

- Given in combination with remdesivir in hospitalized patients with COVID pneumonia
- Can be given in non hypoxemic patients or in hypoxemic patients Spo2 , 94% combination with recommended dose of steroid)
- Can be given in patients with or without raised inflammatory markers

P H A R M A C O K I N E T I C S / PHARMACODYNAMICS

ABSORPTION: After oral administration, baricitinib is rapidly absorbed reaching peak plasma concentrations within 60 minutes. The absolute bioavailability is 80%.

METABOLISM: Baricitinib undergoes oxidation by CYP3A4, although less than 10% of the total dose is prone to this biotransformation. There is no formation of quantifiable metabolites in the plasma.

ELIMINATION: Baricitinib is primarily cleared by renal elimination through both filtration and active secretion. Approximately 75% is excreted in the urine (69% unchanged) and 20% in the feces (15% unchanged) The half-life is 6–9 hours in healthy volunteers but increases to 12 hours in patients with RA and 19 hours in subjects with severe renal impairment or ESRD.

DRUG-INTERACTIONS:

Strong OAT3 Inhibitors: Baricitinib exposure is increased when baricitinib is co administered

with strong OAT3 inhibitors (such as probenecid). In patients taking strong OAT3 inhibitors, such as probenecid, reduce the recommended dose as follows:

- If the recommended dose is 4 mg once daily, reduce dose to 2 mg once daily.
- If the recommended dose is 2 mg once daily, reduce dose to 1 mg once daily.
- If the recommended dose is 1 mg once daily, consider discontinuing probenecid

Other JAK Inhibitors or biologic disease modifying anti-rheumatic drugs (DMARDs): Baricitinib has not been studied in combination with other JAK inhibitors or with biologic DMARDs (biologic treatments targeting cytokines, B-cells, or T-cells) and is not recommended.

Side effects of the drug with long term use of Baricitinib

- Venous thromboembolism
- Arterial thrombosis
- GI perforation
- Pulmonary embolism
- Other infectious diseases
- Nausea
- raised ALT/SGPT level
- Raised aspartate aminotransferase levels
- Upper respiratory infections
- hyperglycaemia,
- anaemia,
- decreased lymphocyte count, and
- acute kidney injury
- Hypersensitivity reactions

Despite the concerns of increased side effects of infections, thrombosis with baricitinib there was no increased incidence of side effects in

ACTT 2 trial. In fact in the combination arm which received Remdesivir and Baricitinib there was decreased incidence of side effects compared to Remdesivir alone.

Overall Baricitinib has a very good safety profile with good therapeutic benefit in patients with COVID-19 pneumonia with faster improvement of hypoxemia, inflammatory markers and decreased incidence of new onset hypoxemia.

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Tocilizumab in COVID 19

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Introduction

Tocilizumab is a monoclonal antibody against the Interleukin - 6 (IL-6) receptor. It is an immunosuppressive drug that was originally used in the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis.

IL-6 in COVID-19

COVID-19 is associated with a dysregulated immune response along with hyperinflammation due to a 'cytokine storm'. High levels of IL-6 have been associated with cases of severe COVID-19. In addition, elevated IL-6 levels were also found to be predictive of the likelihood of mechanical ventilation. Its use proliferated after early observations from China showed increased risk of death in patients with COVID-19 and elevated IL-6 levels, and nonrandomized studies suggested benefit from tocilizumab treatment.

Evidence Based Medicine Recommendations For Tocilizumab Use In COVID-19

1. **Tocilizumab Treatment For Cytokine Release Syndrome In Hospitalised Patients With Coronavirus Disease 2019 - Chest Journal, June 2020**

Early evidence came in the form of this observational study from the United States which found that tocilizumab treated patients had a lower-than-expected mortality in the subgroup with cytokine release syndrome. In tocilizumab-treated patients, oxygenation and inflammatory biomarkers improved, with higher than

expected survival.

2. **Tocilizumab In Patients With Severe COVID-19 - The Lancet Rheumatology, June 2020**

This retrospective observational study from Italy found similar results and concluded that intravenous or subcutaneously administered tocilizumab may reduce the risk of mechanical ventilation or death in patients with severe COVID-19 pneumonia.

3. **Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19 - Oct 2020, JAMA Internal Medicine**

The STOP-COVID tocilizumab study stands out owing to its large sample size and focus on patients admitted to intensive care units (ICUs) at leading academic centers across the United States. The investigators used observational data from a large, multisite study along with adjustment for confounding factors and found a reduced time to death and risk of death at 30 days in patients treated with tocilizumab.

4. **Efficacy of Tocilizumab in Patients Hospitalized with Covid-19 - Dec 2020, New England Journal of Medicine**

In this randomized, double-blind, placebo-controlled trial, the researchers did not find any efficacy of interleukin-6 receptor blockade for the treatment of hospitalized patients with COVID-19. Tocilizumab was

not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19.

5. Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia - Jan 2021, New England Journal of Medicine

The EMPACTA trial was a global, randomized, double-blind, placebo-controlled, phase-3 trial with the aim to evaluate the safety and efficacy of tocilizumab in hospitalized COVID -19 patients who were not on mechanical ventilation. The findings from this study supported the benefit of tocilizumab in reducing the progression of these patients to the composite outcome of mechanical ventilation or death but it did not find a survival benefit.

6. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - April 2021, New England Journal of Medicine

Preliminary results from the REMAP-CAP international adaptive trial evaluated efficacy of tocilizumab 8 mg/kg, sarilumab 400 mg, or control in critically ill hospitalized adults receiving organ support in intensive care. They found that the estimates of treatment effect for patients treated with either tocilizumab or sarilumab and corticosteroids in combination were greater than for any single intervention. Of note, corticosteroids became part of the standard of care midway through the trial. They concluded that treatment with IL-6 receptor antagonists like tocilizumab and sarilumab improved outcomes including survival in critically ill COVID-19 patients.

7. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open label, platform trial - May 2021, The Lancet

The RECOVERY trial from the UK found a clear mortality benefit in the patients receiving tocilizumab along with systemic steroids. Patients in the tocilizumab group were more likely to be discharged from the hospital within 28 days. Among those not receiving invasive mechanical ventilation at baseline, patients who received tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death

National Institutes of Health Recommendation

The Panel recommends using **tocilizumab (single intravenous [IV] dose of 8 mg/kg actual body weight up to 800 mg) in combination with Dexamethasone (6 mg daily for up to 10 days)** in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:

- Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal cannula (HFNC) oxygen ($>0.4 \text{ FiO}_2/30 \text{ L/min}$ of oxygen flow) (BIIa); or
- Recently hospitalized patients (i.e., within the first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP $>75 \text{ mg/L}$) (BIIa).

Contraindications

- Significantly immunocompromised individuals
- ALT levels greater than 5 times the upper limit of normal

- Patients with high risk of GI perforation
- Uncontrolled serious bacterial, fungal or non-SARS-CoV-2 viral infection
- ANC lesser than 500 cells/ µL or a platelet count less than 50,000 cells/ µL
- Patients with known hypersensitivity to tocilizumab.

Experience at AIG with Tocilizumab in COVID-19 patients

- Total number of patients who received tocilizumab - 47
- Median age of patients - 57 years (27-86 years)
- Gender distribution - 40 male, 7 female
- Median APACHE score - 11
- Median ICU stay - 7.5 days (1-24 days)
- Median hospital stay - 13 days (2-51 days)
- Timing of tocilizumab dosage - between first and second week of illness
- Median IL-6 levels - 126.8 (normal <7)
- Median P/F ratio - 114 (normal 400-500)
- Ventilator - 30/47 (67%)
- NIV/HFNC - 17/47 (33%)
- Sepsis - 18/47 (38%)
- Septic shock - 10/47 (21%)
- Mortality - 23/47 (49%)
- Discharged patients - 24/47 (51%)

Conclusion

- Tocilizumab may be beneficial in the initial period of illness (within 7-10 days)
- IL-6 levels should be more than 25-50 times of normal range for consideration of Tocilizumab use.
- Sepsis should be ruled out before initiating treatment (cultures and procalcitonin should be negative)
- Recent studies are in favour of its use in

the acute setting especially among younger patients without comorbidities who were found to respond better to it.

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Role of Convalescent Plasma, IvIg, ECMO, Cytosorb, Lung Transplantation in COVID 19

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INTRODUCTION :

COVID - 19 disease is a syndrome spectrum caused by SARS-COV-2 (Severe Acute Respiratory Syndrome - Corona virus -2). (1).Presentation ranges from being asymptomatic, minor upper respiratory tract infection to multi organ failure requiring intensive care support and death. Different variants of this virus have been recognised and current variant of concern (VOC) is labelled as Delta variant , first discovered in India. (2). From therapeutic point of view, the clinical course is divided into early viraemia and later inappropriate hyperimmune host response needing intensive care and adjuvant support. [Fig 1.](3). The complex interplay of virus and host response, with no absolute clinical or laboratory demarcation, makes the timing of a specific therapy challenging. For example, antiviral agent should be used during viremia phase and anti inflammatory agents during hyperimmune response (aka cytokine storm) phase. But there are no clinical criteria or laboratory test to demarcate occurrence of each phase, so that a specific therapy can be applied. In fact, there is a considerable overlap with these phases, leading to multi dimensional challenge for treating covid-19 syndrome.

While a range of therapeutics have been proposed for management of COVID-19, this article will focus on current role of Covalescent plasma, Immunoglobulin, Extracorporeal therapies and lung transplant in management of COVID19 disease.

CONVALESCENT PLASMA :

RATIONALE :

Infusing passive immunity using blood serum from immunised host has been known for more than a century. Plasma from a patient who has survived a previous infection and developed antibodies against the pathogen responsible is used to neutralise the pathogen and achieve short term immunity. The use of passive antibodies from plasma in COVID-19, is extrapolation from the previous successful treatment of SARS,H1N1,H5N1 avian flu and severe acute respiratory infections (SARI) as the virological and clinical characteristics share similarity of these viruses with covid 19.

Anti SARS -CoV IgM and IgG in convalescent plasma directly neutralises the free virus preventing its entry into cell, inhibit replication , decreases infectivity and infected cell immune clearance and complement activation. It also causes antibody dependent cellular

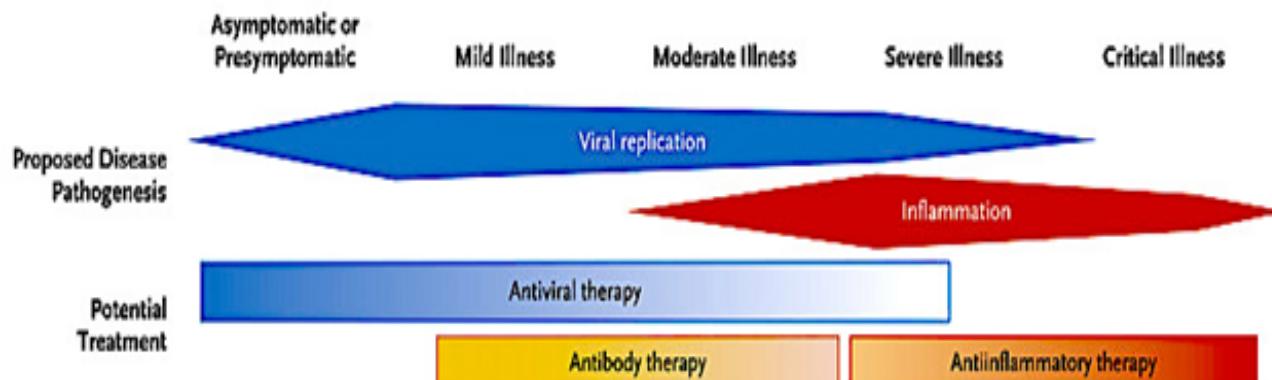


Figure 1 : Legend : Pathophysiological Course of COVID19 disease and therapeutic option.

toxicity and phagocytosis. It provides short term humoral immunity.

THERAPY :

Patients eligibility and Donor's eligibility criteria have been developed. These criteria are government or medical society specific. Generally, following criteria are followed:

A. Patient eligibility -

1. Laboratory confirmed covid 19
2. Severe or life threatening covid 19
3. Informed consent provided by patient or health care proxy

B. Donor Eligibility :

Evidence of COVID 19 infection documented by a laboratory test either by :

1. A diagnostic test (eg., nasopharyngeal swab) at the time of illness OR
2. A positive serological test for SARS -COV -2 antibodies after recovery, if prior diagnostic testing was not performed at the time when covid -19 was suspected.

And Either one of the following:

- i. Complete resolution of symptoms at least 28 days prior to donation OR
- ii. Complete resolution of symptoms at least 14 days prior to donation AND
- iii. Negative results for COVID -19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.

Male donors or female donors (who are not pregnant) or female donors who have been tested since most recent pregnancy and results interpreted for HLA antibodies.

Presence of SARS -COV- 2 neutralizing antibody titres The donor should preferably live in the same area as the intended recipient Donor screening and conventional viral testing (HIV, HCV and HBV NAT)

DOSE :

Donor's IgG against SARS-CoV-2 spike (S) protein titres measurement is recommended for therapeutic plasma administration. There are no fixed IgG levels

recommended. However (see later), evidence suggest use of High titre plasma (> 1:250) over low titre plasma.

There is no evidence regarding use of number of units of plasma. There is variability in units used in various trials. Majority of trial have used 1-2 units (250 ml each) of convalescent plasma.

EVIDENCE :

The major trials like RECOVERY, REMAP-CAP failed to show mortality or any clinical benefit. However, all of these trial have been criticised for their procedural inconsistencies, lack of standardised non pharmaceutical measures and plasma used having with low titres.(4). Study published in NEJM (5.) and targeting Elderly (>75 yrs) population or more than 65 yrs with comorbidites, used 250ml of plasma with High IgG titres (>1:1000) against SARS-CoV-2 spike (S) protein. The study concluded with some advantage, though not statistically significant, of plasma over placebo when used early (< 72 hours of onset of symptoms) and having high titres. There was trend towards decrease in progression to severe disease from mild disease and no serious adverse events were observed. The effect was dose dependent to antibody titers.

GUIDELINES

FDA, in absence of totality of evidence, benefits of plasma outweighs risks and grants emergency use authorisation (EUA) for plasma to be used in hospitalised patients with progressive infection. But recommends against using plasma with low titres and use in severe hospitalised patients on mechanical ventilators. National Institutes of Health(NIH) guidelines says insufficient data to recommend for or against the use of convalescent plasma. IDSA and American Blood bank association, restricts its use in clinical trials.

AUTHOR OPINION

Convalescent plasma can be safely used in mild covid19 disease to prevent the progression, provided following criteria are met : Early use (< 72 hours of symptoms), High titres of IgG (> 1:250) - higher the better, and in age group 65-75 years of age. One to two units is recommended.

IMMUNOGLOBULINS:

RATIONALE

IVIG (Intra Venous Immunoglobulin G) is a concentrate of IgG immunoglobulins, derived from pooled plasma of many healthy volunteers recovered from viral infection. The role of IVIG in COVID19 is again extrapolation from its use in previous viral infections like SARS, Ebola, Middle East respiratory syndrome (MERS), West Nile Fever (WNF) and Influenza H1N1.(6)(7)(8)(9)(10)(11) IVIG protects against virus with various mechanisms. One is direct neutralising effect on virus by promoting opsonisation thus eliminating the virus by phagocytes and another is binding to neutrophils and monocytes and decreasing the inflammation, thus causing anti inflammatory effect. (12).

Further, possible therapeutic effect of IVIG is considered in prevention of pulmonary fibrosis as sequel of severe COVID19 pneumonia. Macrophages are one of the important defence of alveolar inflammation and has property of promoting fibroblast activation and cause healing by fibrosis.(13) With proposed anti inflammatory effect by suppressing phagocytes (including macrophages),(14) IVIG may be useful in prevention of fibrosis sequel of COVID19. Precise mechanism and evidence is lacking for this hypothesis.

Lastly, IVIG has also been therapeutic in management of Vaccine Induced Thrombotic Thrombocytopenia (VITT). VITT is a rare thrombotic disorder found post vaccination with adenoviral vector vaccine administration. (Astrazeneca vaccine).The mechanism involves the production of IgG antibodies that recognise and activate platelet factor 4 (PF4) via Fc γ IIa receptors, causing thrombocytopenia (platelet consumption) and activation of coagulation. (15)(16)(17)(18)(19). The disorder resembles closely with Heparin induced thrombocytopenia (HIT). Intravenous immune globulin (IVIG) competitively inhibits the binding of VITT IgG antibodies with the platelet Fc γ IIa receptors, thus reducing platelet activation.This may be an important treatment consideration for VITT management.

THERAPY AND DOSE

The dose used in various trials for anti inflammatory effect ranged from 0.3- 0.5g/kg/day for 3-5 days. There is no consistency among various trials in using a unified dose.(20).

Dose recommendation for management of VITT was 1 g/kg over 2 days, based on platelet response.(21)

EVIDENCE

As per the latest meta-analysis published in June 2021, only 7 quality evidence were recognised from total of more than 5000 articles scanned .(20). Out of 7, 4 were clinical trials and 3 cohort studies, with total 825 hospitalised patient. None of the trials or studies were high quality and hence the results need to be interpreted with caution. The meta analysis concluded that there is a possibility that high dose IVIG has clinical efficacy in decreasing the mortality and increasing hospital length of stay. The therapy is effective when administered early [< 48 hours of hospitalization (22)] in critically ill and severe covid19 patients.

There is no evidence so far to say use of IVIG is useful in prevention of fibrosis in covid19 disease.

Several case reports supports the use of high dose IVIG in treatment of VITT.(21)

CURRENT GUIDELINES

FDA, NIH, IDSA and Surviving sepsis guidelines currently recommends against the use of IVIG except for clinical trials.(23)(24)(25). Even the major trial evaluating various therapies like SOLIDARITY, REMAP-CAP, DisCoVery trial has not included IVIG as treatment of interest.

AUTHORS OPINION

Considering the cost of IVIG in India, its non specificity for SARS-COV-2, it should not be administered to patients as treatment for COVID19 disease.

IVIG is recommended as treatment of VITT(Vaccine Induced Thrombotic Thrombocytopenia) in dose of 1g/kg for 2 days and additional dose of 0.5-1 g/kg for inadequate response or relapse of thrombocytopenia. (26)

EXTRACORPOREAL HAEMADSORBTION :

RATIONALE :

During later phase of hyperimmune host response, patients with COVID19 develop what is described as "Cytokine storm" or "hyper inflammatory syndrome" or "Cytokine release syndrome" which eventually leads to multi organ failure and death. This is similar to sepsis, septic shock, ARDS (non covid related) and chimeric antigen receptor -T cell induced cytokine release syndrome (CAR-T CRS). However, studies have shown that the inflammatory cytokine levels are much lower in COVID19 patients than said situations.(27). Extracorporeal blood purification techniques have been proposed as an adjuvant therapy in this hyper immune phase of COVID19 patients. The potential role of extracorporeal blood purification in critically ill patients with COVID19 is in removal of inflammatory cytokines, damage associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), including endotoxins and SARS-CoV-2 particles that contribute to the development of multiple organ failure and mortality. Besides removal of these anti-inflammatory agents, these techniques are also useful in removal of urea, creatinine, correction of electrolytes and acid-base balance, water balance and correction of fluid overload state and management of hyperthermia.(28)

These extracorporeal blood purification techniques include therapeutic plasma exchange, hemoperfusion using sorbents (e.g Cytosorb), continuous renal replacement therapy (CRRT) with special filters, and high-dose CRRT with different size membranes.(29). Hemoperfusion can remove inflammatory targets, DAMPs, PAMPs and SARS-CoV-2 particles, Plasma exchange can remove inflammatory mediators and hyper-coagulable proteins, CRRT with special filters can remove target molecules by adsorption and High dose CRRT can remove targeted molecules by diffusion and convection. (30)

THERAPY :

Setting up of extracorporeal therapy is essentially starting a dialysis for patients meeting the AKI

criteria. CRRT requires special machine and dose is adjusted as per clinical and biochemical parameters of patient.

Special filters for haemadsorption are attached in sequence with the regular filter in CRRT machine. These Haemadsorption filters can also be used on regular dialysis machines (non - CRRT) if hemodynamics of patients permit. Specific duration of use of filters is as per manufacturers guidelines. Generally, 12 - 24 hour session is recommended. The efficacy is determined by dropping levels of measured inflammatory markers, but due to limited availability of these tests clinical parameters like decreasing vasopressor requirements, improving oxygenation are used as surrogates.

EVIDENCE :

Most of the current data for use of extracorporeal therapy is from critically ill COVID19 patients with hemodynamic instability, needing renal replacement therapy and severe ARDS requiring ECMO.(31).(32)(33). So far, no high quality trials have shown mortality or any clinical benefit for use of extracorporeal therapies in the cytokine release syndromes (septic shock, ARDS etc).(34)(35)(36). So, even if we consider, cytokine storm as base for covid19 multi organ failure, extracorporeal blood purification does not offer evidence based consistent clinical efficacy.(37)

GUIDELINES

None of the published guidelines for management of critically ill covid19 patients includes extracorporeal blood purification techniques. FDA has suggested use of Haemadsorption cartridge under emergency use authorisation (EUA) in selected group of patients, while NHS gives no recommendation for or against use.

AUTHORS OPINION

While there is no good evidence of using blood purification techniques causing clinical improvement, in critically ill covid19 patient with multi organ dysfunction, requiring renal replacement therapy or ECMO, it will be worthwhile using haemadsorption cartridge ,provided resources and finances are adequate. It is an experimental

technique, with no major adverse events so far reported in literature and should be used as one of the last resorts.

EXTRACORPOREAL MEMBRANE OXYGENATION

RATIONALE

The pneumonia caused by COVID19 can lead to profound hypoxemia and ARDS. Berlin definition classify the ARDS based on severity of hypoxemia defined as $\text{PaO}_2/\text{FiO}_2$ (p/f) ratio. Accordingly, ARDS is mild ($200 < \text{p/f} < 300$), moderate ($200 < \text{p/f} < 100$), and severe (< 100). (38). The standard treatment proposed includes lung protective mechanical ventilation strategy, using high peep, short term use of neuromuscular block, and prone positioning based on increasing severity of hypoxemia.(39). Certain adjuvant therapies are reserved for severe hypoxia not responding to this standard therapy and include inhaled prostacyclin, inhaled nitric oxides and Extracorporeal membrane oxygenation (ECMO). With the growing number of facilities, ECMO has been the most popular adjuvant therapy for refractory hypoxemia and severe ARDS, not responding to the standard therapies. As with other aetiologies, use of ECMO has been extrapolated to COVID19 induced severe ARDS, after the standard therapies have failed.

THERAPY

ECMO constitutes circulating venous blood of patient through an oxygenator, where blood is oxygenated and carbon dioxide removed, and circulating back either to right ventricle or central aorta. The therapy has essentially evolved from cardiac bypass in theatres to bed-side in ICU. (40). Based on returning of the blood, ECMO are classified as Veno-Venous (blood returns to right side of heart), and Veno-Arterial (Where blood returns to central aorta). Veno-Venous (VV ECMO) are used for pure respiratory failure with normal heart function and Veno-Arterial (VA ECMO) is used for respiratory and cardiac failure indication.(40). Mostly in ARDS, VV ECMO is preferred.

Indication and Contraindications for initiation of ECMO in COVID19 ARDS is same as for other aetiologies. We refer to ELSO guidelines or other established literature for same. (41)

Contraindication for ECMO:

Relative Contraindications

- Age ≥ 65
- Obesity BMI > 40
- Immunocompromised status
- No Legal Decision maker
- Advanced Heart failure
- Very High dose vasopressors, cannot be considered for any kind of ECMO

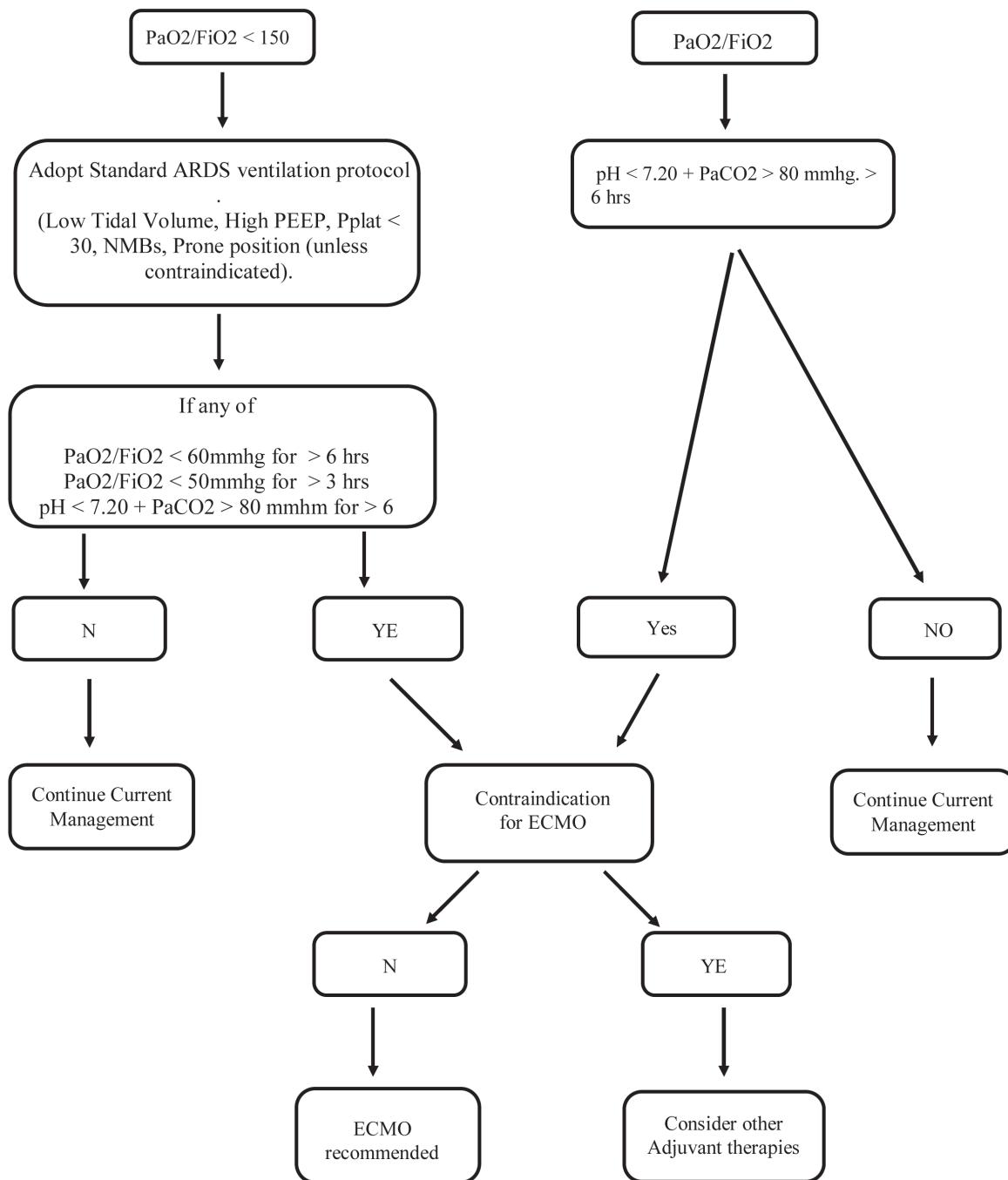
Absolute Contraindication

- Advanced age
- Clinical Frailty Scale Category ≥ 3
- Mechanical Ventilation > 10 days with CKD $>$ stage 3
- Cirrhosis
- Dementia
- Poor baseline neurology
- Malignancy
- Uncontrolled diabetes with end organ damage
- Severe reconditioning
- Protein Energy Malnutrition
- Severe Peripheral vascular disease
- Life expectancy poor
- Non ambulatory or unable to perform activities
- Severe Multi Organ Failure
- Severe Brain Injury
- Uncontrollable Coagulopathy
- Ongoing CPR

BMI, body mass index ; CKD, chronic kidney disease; CPR, cardio pulmonary resuscitation; ECMO, Extracorporeal membrane oxygenation; VA, Veno Arterial; Vv, Veno Venus.

Indication for VA ECMO in COVID19 is limited to associated cardiovascular complications, refractory cardiogenic shock in particular. Upto 22% of ICU care COVID 19 patients have been noted to have direct or indirect myocardial injury in form of venous

FLOW CHART 1. Indication for ECMO.



thromboembolism, acute myocardial infarction and myocarditis. (42) (43)(44). Timely provision of VA ECMO is recommended before development of multi-organ failure.

Indication for hybrid therapy of VV-A ECMO is also a possibility with mixed respiratory and cardiac indication and need to be carried out in experienced centres only.

ECMO is a resource intense therapy which require multidisciplinary team for its initiation, maintainance and weaning. Institutions without a well-established ECMO program should not attempt to initiate a new program during a pandemic.A multidisciplinary team that includes surgeons, intensivists, anaesthesiologists as well as ECMO trained nurses, respiratory therapists, and/or perfusionist technologists who have previously worked together

managing ECMO patients is critically important. Availability of durable and disposable equipments and decontamination of ECMO equipment is necessary during the pandemic. For infection control purpose, availability of single intensive care unit for COVID19 patient on ECMO support is highly recommended to reduce the exposure of additional medical professional.

Details of each of planning, initiation, maintenance and weaning, recognition and management of complications and adjuvant strategies are well described in ELSO society guidelines and we recommend strict adherence to same.(41)

EVIDENCE

Current evidence of improving mortality with ECMO is very poor. Initial data from middle east and India showed more than 50% mortality in patients on ECMO.(45). Study from France showed mortality of 54% (46). Largest registry of ECMO patients (ELSO group) have reported mortality of 47% in first wave and 54% in second wave in patients who were offered ECMO. (47).

Another group, The ECMOVIBER (use of ECMO during the coVid-19 pandemic in the IBERian peninsula) (48), have analysed the high mortality trend from various sources. According to the analysis, higher mortality was related to increased use of ECMO at less experienced centre, more co-infection and delayed intubation.

In one of French follow up study of patients on ECMO, 12 patients had recovery after 50 days or more, 6 (~ 50%) were alive and weaned off ECMO after 90 days. (49). This indicates that patients may still recover late and not necessarily end up with end stage pulmonary fibrosis. But there are no objective criteria or prediction model for such outcome.

GUIDELINES

None of the society currently have sufficient evidence to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in adults with COVID-19 and refractory hypoxemia.

AUTHORS OPINION :

ECMO should be kept as a last rescue therapy after lung protective ventilation, high positive end-expiratory pressure (PEEP), recruitment manoeuvres, neuromuscular blocking agents and prone positioning have failed. We recommend strictly adhering to indications and contra-indications as per ELSO guidelines (41) while selecting patients. ECMO is a highly specialised therapy, requiring multidisciplinary team of ECMO trained personnel. Studies have shown adverse high mortality in a low volume, new ECMO centres. Hence, we caution the use of ECMO in new centres and recommend transfer of patients to high well trained ECMO centre.

ECMO can be considered as bridge to transplant in end stage fibrosis, a well documented sequel of COVID19 ARDS.

LUNG TRANSPLANT in COVID19 :

RATIONALE :

One of the consequence of severe covid19 pneumonia is progression to lung fibrosis. Early reports from China, revealed that features and the risk factors among the cohort with severe COVID19 infection were also present in patients suffering with idiopathic pulmonary fibrosis (IPF).(50). These clinical findings were also substantiated with histological findings of extrasplanted lung from patient with severe COVID19 pneumonia.(51). Although use of anti fibrotic therapies have been discussed (52), lung transplant remains the only option for improved outcome. It should be noted that generally, lung transplant is not recommended for lung injury due to infectious cause.(53)

THERAPY

Cypel et al has described some consideration regarding potential candidacy for lung transplant in COVID19 ARDS.(54). These consideration factors are likely to increase the chance of a successful outcome.

1. Age less than 65 years. Current evidence from ECMO bridge to lung transplantation shows high mortality for elderly patients.
2. Single-organ dysfunction.

3. Sufficient time should be allowed for lung recovery. This is the most contentious point. How long one must wait is not clearly defined. It is always better to able to survive without transplant given its suboptimal survival rate. Observations from previous outbreaks have shown several weeks to months on ECMO before complete recovery has occurred.(55). Whether these can be extrapolated to COVID-19 remains unknown. Authors of the article recommends waiting period of 4-6 weeks before transplant is considered.(54).
4. Irreversible lung damage should be demonstrated radiologically.
5. Patient should be neurologically sound enough to discuss transplant and give consent as post transplant life is difficult and patient should be psychologically prepared.
6. Other organ system should be in good condition and patient should be able to participate in pre-surgical physiotherapy.
7. Typical criteria for transplantation like BMI, absence of other comorbidites should be fulfilled.(56)
8. There should be evidence of absence of any viable SARS-CoV-2 virus. For that PCR test should be negative. Evidence show that even asymptomatic PCR positive patients have very high mortality.(57).
9. Transplant should occur only in high experience centres considering the complexity involved.

Once these criteria are fulfilled, patient should be referred to the transplant centre. Details of transplant procedure and follow up is beyond the scope of this article and hence will not be discussed.

EVIDENCE :

There is extremely limited evidence in literature regarding lung transplant success in COVID19 patients. There are no control trials but only case reports and case series. Demographic factors and timing of transplant need to be validated. As the

pandemic progresses, more evidence is expected.

One of the early transplant case series is reported by Bharat et al.(58). The team reported 12 cases from different countries. There was 100% survival at 30 days, while 1 patient died due to severe critical illness neuromyopathy and secondary infection on follow up of 80 days. Lang et al. (59.) have earlier reported a single case where transplant was done when PCR was positive. The author mentions that the lung transplantation can be done in patients with positive RT-PCR results, provided that Vero cell cultures confirm non-infectivity. Han et al, reported 2 cases of lung transplant in elderly patients (Aged 66 and 70) with successful outcome.(60). Chen et al.(61)reported 3 cases (Aged 66, 58 and 73 years), with successful outcome of two and death of 1 on first post op day.

GUIDELINES :

Currently no society or body recommend for or against lung transplantation due to lack of evidence. Its at discretion of treating physician, availability of expertise and resources for lung transplantation.

AUTHORS OPINION :

Lung transplant, is an extremely specialised branch and is expensive with best of 5 year survival rate of 60%. It requires special skills, expertise and resources. While lung transplant is not recommended in acute cases due to infectious disease (53), uncertainty in natural course in COVID19 ARDS has led to some early successful lung transplant as per case reports. With no where to go and as a last option, and with availability of expertise and resource, lung transplant can be considered.

CONCLUSION :

Severe COVID19 disease continues to have a very high mortality rate. Despite therapies like steroids, anti coagulation and anti inflammatory medications been approved with randomised controlled trials, still a large deficit remains in its treatment. Convalescent plasma, Immunoglobulin, extracorporeal haemadsorption, ECMO and Lung transplant, showed some promising start but haven't found their place in guidelines due to poor

quality of evidence. These methods have a strong pathophysiological basis for its usage as rescue therapy in severe COVID19. With strict selection criteria and weighing risk against benefit, these therapies can be used to decrease the mortality in severe ARDS due to COVID19, till a formal, good quality, randomised control trials endorse it.

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COVID Vaccinology

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Introduction

Even today, with all the extensive research, it is difficult to predict what kind of vaccine can be truly effective for the disease. This difficulty is even bigger for COVID-19, as it is a new disease and ongoing studies in worldwide are adding new data at a tremendous pace.

Fair and reasonable access to effective and safe vaccines is very important in controlling the COVID-19 pandemic, so it is hugely encouraging to see so many vaccines proving and going into development.

The coronavirus responsible for COVID-19 (SARS-CoV2) is an RNA virus, and these RNA viruses generally have comparatively high mutation rate. This is the reason behind the fact that genetic instability has always been considered as a challenge to develop effective vaccines against RNA viruses.

Mode of action of vaccine

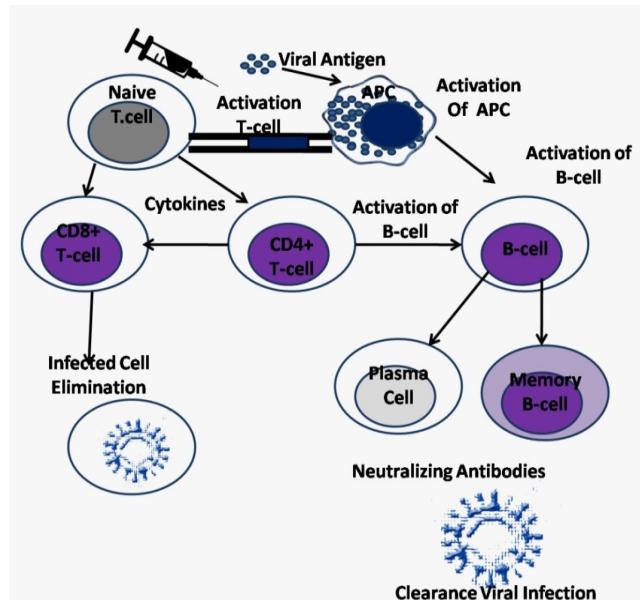


Figure 1: Vaccine mode of Action

Viral antigen given as vaccine got engulfed by antigen presenting cells (APC). These APCs will present the antigen on its surface which has been recognized by the B cells, leading to the activation of B CELLS. Finally B cells transforms into the clone of plasma cells and some memory cells. These memory cells will take care of further viral infections. While the clone of plasma cells will produce the antibody, which fights COVID 19 virus.

Types of covid 19 vaccine

There are four types of covid 19 vaccines

1. Whole viruses are used to trigger an immune Response

a. Live attenuated virus – risk of Multiplication & infection in weak immune system. Not yet available Eg: Live measles viral platform

b. Killed & inactivated vaccines : Cannot replicate but immune response is good. Eg. Covaxin

2. Protein Subunits

Fragments of Protein are used to trigger immune response. Side effects are minimum but immune response may be weaker- will need Boosters. Eg: Novavax

3. Nucleic Acid

Genetic Material is either RNA or DNA. They provide cells with the instruction to make the Antigen. Usually Spike Protein in COVID. This Genetic Material gets into cells & uses the cells' protein to make the Antigen that will trigger Immune response. It is easy to make and cheap. Immune Response is strong.

Regulatory approaches are tough & RNA vaccine to be kept at ultracold Temp -70°. No approval received yet for it.

4. Viral vector

Same genetic instruction to produce antigens & Immunity. But uses a harmless virus as Adenovirus of common cold. Mimics natural viral infection & evokes strong Immune Response. Since many are already infected by cold and cough, the vaccine may be less effective in those. Eg : Covishield (Oxford) (**Fig 2 see Color pages section**)

COVID Vaccines

'GERMAN-US' vaccine: Pfizer-BioNTech; BNT162b2; New messenger RNA (mRNA) platform* - for spike protein; 90% efficacy; storage .. minus 70 degrees Celsius; Rs. 1,500 per dose; available in the UK & elsewhere from December 2020.

'US' vaccine: Moderna; mRNA-1273 for spike protein; New messenger RNA (mRNA) platform*; 95% efficacy; storage .. minus 40 degrees Celsius; Rs. 2,775 per dose.

'British' vaccine: Oxford-AstraZeneca; ChAdOx1 nCoV19 / Covishield; Traditional inactivated virus platform – Adenovirus from Chimpanzee; 70% efficacy; storage .. 2 to 8 degrees Celsius; Rs. 600 per dose; Supply prioritised to India; 10 crore doses by January 2021 ; Manufactured under license by Serum Institute of India; 500 million doses ordered by India; 40 million doses ready under the 'risk-manufacturing license'.

'Russian' vaccine: Gamaleya Institute; Sputnik V; Two human adenoviruses vector platforms; 95% efficacy; Free of cost for Russians; Partnered by Dr. Reddy's Laboratories, Hyderabad; Available in India by May 2021; 100 million doses ordered by India. A prediction of protection up to 2 years is reported.

Vaccine Antibodies¹

1. Types of antibodies produced after natural COVID infection could be different – it could be either – Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) and therefore total IgG antibody titre would be high.
2. These antibodies are different from antibody produced by different vaccines. Depending upon the types of vaccine used antibody

produced by different vaccines could be different.

3. While Moderna Pfizer and Oxford AZ vaccine are directed towards spike antigen it would produce anti spike antibody, live attenuated full virus vaccine such as Covaxin should produce all antibodies. Hence physicians should be on alert when testing for antibody titre after two different vaccine.
 - No standard protocol at present having validated laboratory test to detect neutralising postvaccination antibody exists.
 - Laboratory results must mention COVID IgG against spike protein.
 - Neutralising Antibodies-NAB
 - Non Neutralising Antibody-NNAb. Infectivity may be enhanced by this, because antibodies can interact with the receptors on macrophages. By the process of endocytosis the entire virus-antibody complex is brought into the cell.

Post-vaccination antibodies and efficacy²

Corona virus genome encodes 4 structural protein

1. Spike (S) — The S protein is very large trans membrane protein. It consists as trimers to form a distinctive SURFACE SPIKES of corona virus.
2. Envelop(E).
3. Membrane(M).
4. Nucleocapsid(N).

IgA and IgM levels start decreasing after 60 days of onset of symptoms, though IgG levels remain significant. IgG antibodies persist up to 90 days, even in mild cases.

Higher levels of antibodies are found in Patients with severe COVID-19 than those with mild/ asymptomatic cases, but the kinetics of antibody levels are similar across all cases.

Neutralising antibodies are induced by Available vaccines to the spike protein and also cellular immune responses. Those patients with severe COVID-19 are having higher Titers of neutralizing

antibodies up to seven times higher than in those with a mild disease.

How can we determine if the antibodies being detected by common serology assays are capable of neutralizing SARS-CoV-2?

Neutralizing antibodies (NAb) are a subset of antibodies produced against a virus that independently restricts viral entry into host cells and that is primarily of the IgG isotype.

Plaque reduction neutralisation tests (PRNT) are the "gold-standard" for assessing neutralising Antibody titers (80- 320 being the significant value)

Pseudo typed Vesicular Stomatitis Virus(VSV) expressing SARS-CoV-2 spike (S) protein have been used to develop BSL2 neutralization tests

Vaccination and immunity

SARS-CoV-2 is different in immunological aspect also. Vaccination or infection produces antibodies and T-cell immunity. But in the case of COVID-19 vaccination or infection, the antibodies may be present only for a couple of months while the T-cell immunity may be durable for six months or more.

When a vaccination policy is made not to vaccinate people who have immunity due to previous infection with or without symptoms, tests must be done to detect T-cell immunity rather than the antibodies (antibody tests are being done now), to identify this group of population. But this test is very complicated and very costly.

Cardiff University researchers have now come up with a simplified, cheaper and rapid T-cell immunity test called "T- SPOT test".^{2,3} And, people who were infected by other viruses (common cold viruses, etc. – very common in India) may have T-cell immunity which acts against SARS-CoV-2 virus also (pre-existing / cross-reactive - memory T-cell immunity). This may be the reason for lesser health damage in India due to the novel coronavirus. Also, BCG vaccination may have benefits.

WHO Approval pending

- 'Chinese' vaccines: Sinovac Biotech – 1 vaccine;
- Coronavac; Adenovirus platform;

- Sinopharm – 2 vaccines; 86% efficacy.

INDIAN VACCINES :

'Indian' vaccine: **Bharat Biotech**, Hyderabad / ICMR's National Institute of Virology, Pune; Covaxin; Traditional whole cell inactivated virus platform, fully locally developed from a strain isolated by ICMR-NIV, Pune.

'Indian' vaccine: **Zydus Cadila**, Ahmedabad; ZyCov-D; Molecular Plasmid DNA / Live measles viral strain platform.

'Indian' vaccine: **US-based Novavax** / SII of Pune; Recombinant nanoparticle platform; Likely to be available by July 2021; one billion doses ordered by India. 90% effective including ESCAPE Variants

'Indian' vaccine: **Gennova Biopharmaceuticals**, Pune / US-based HDT Biotech; India's first m-RNA platform; Permitted on 10.12.2020 to do 'human trials'.

Other vaccines that are in the making:

- (1) Biological E (Hyderabad) / Baylor College of Medicine; Dynavax; Ad26, COV2.s Adenovirus.
- (2) Mynva IISc, Bangalore; Mynvax ; Heat-tolerant vaccine; Likely to be available by March 2021.
- (3) Nasal vaccines under development; Produce local IgA antibodies to block the virus at the entry point in the nose. To be instilled through nose.

Vaccines now widely used in India

Covaxin – Bharat Biotech

Covishield – Serum Institute of India

Sputnik V- Dr Reddy's Laboratory



Figure 4: Vaccines given in India

The immune response to SARS-CoV-2 infection³

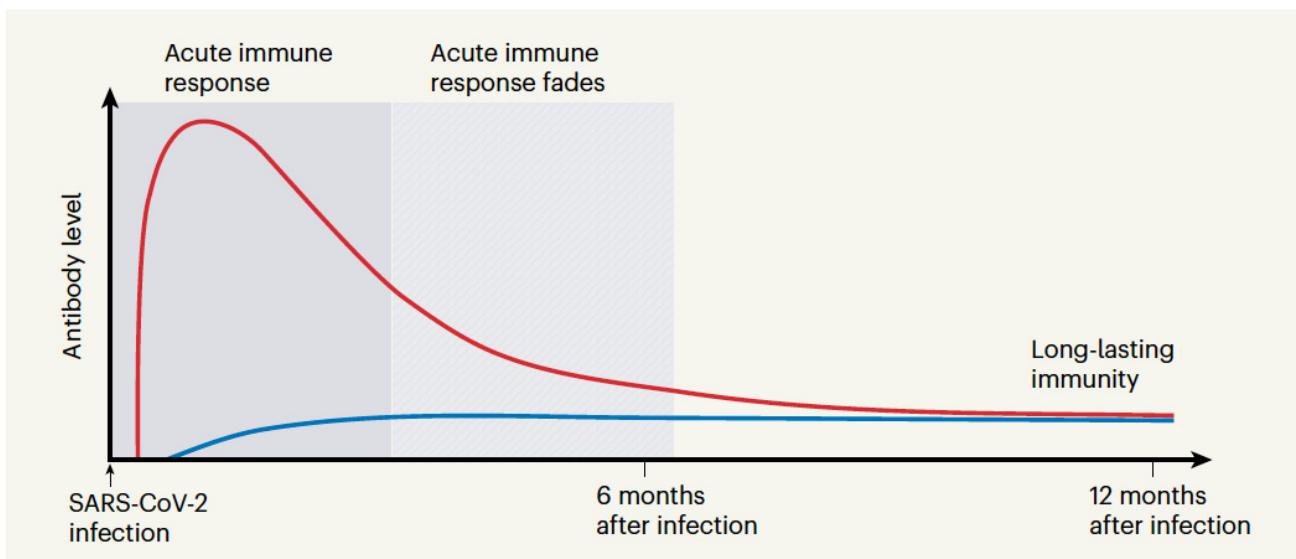


Figure 3 : Antibodies that target viral proteins target (red line). antibody levels peak rapidly during the initial, acute phase of the immune response, this peak is formed by the short-lived immune cells called plasma cells. Antibody producing long-lived, memory plasma cells are generated in the bone marrow. Production of long-term antibody by the cells that gives stable protection at 10–20% level of that during the acute phase (blue line).

Herd immunity⁴

'Herd immunity', also known as 'population immunity', is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection.

Herd immunity against COVID-19 should be achieved by protecting people through vaccination, not by exposing them to the pathogen that causes the disease.

Vaccines train our immune systems to create proteins that fight disease, known as 'antibodies', just as would happen when we are exposed to a disease but – crucially – vaccines work without making us sick. Vaccinated people themselves are protected from getting the infection and also breaking the chain of transmission of pathogen.

Herd Immunity occurs 75 % of the Population are immunized either by Infection or vaccine. For India : 135 cr Population 75 % = 100 crore around. For one positive patient 10 more patient are Positive but not detected. Up to now cases. 3 Crore Test Positive Report (TPR)

Active : $3 \times 10 = 30$ Crore

Vaccinated = 71Crore (50 cr 1st dose. 21cr both doses)

101 Crore (Total)

We need at least 30 crore population to be immunized by vaccination of Two Doses to reach to Herd Immunity & walk without Mask. It is a herculean task but has to be done.

Sero-prevalence: Healthcare workers (HCW)

India : 7,252 HCWs

10.5% HCWs reported not taking vaccine

13.4% HCWs reported receiving one dose

76.1 % HCWs reported receiving two doses

Overall Seroprevalence: 85.2% (95% CI: 83.5 – 86.7)

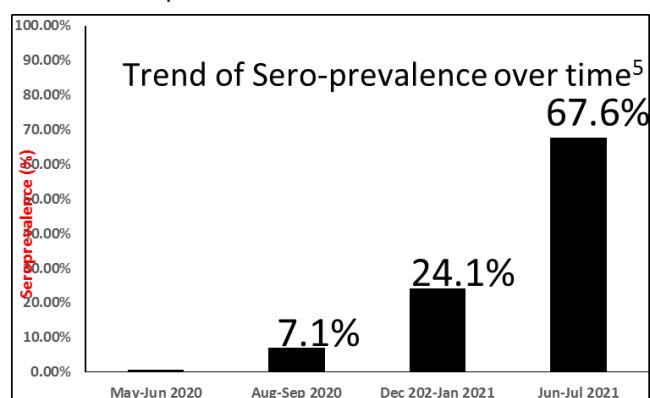


Figure 5: ICMR Fourth National Serosurvey for Covid-19 June – July 2021

Sero-prevalence : As per Vaccination Status :

Status	(%)	(95% CI)
Unvaccinated	62.3	(60.9 - 63.7)
Vaccine (1 dose)	81.0	(79.6 - 82.3)
Vaccine (2 doses)	89.8	(88.4 - 91.1)

Serosurvey Conclusions

- SARS-CoV-2 antibodies are found in two third of the general population.
- One third of population does not have antibodies (which means Still ~ 40 crores are vulnerable)
- Areas/ districts/States without antibodies have the risk of infection waves.
- Both rural and urban areas have similar Sero-prevalence.
- 85% HCWs had antibodies against SARS-CoV-2 .
- One tenth of the HCWs were unvaccinated.

Covishield vs Covaxin comparison:

Covishield is a viral vector vaccine. a weakened, non-replicating strain of Chimpanzee cold virus (adenovirus) is used to carry genetic material of the spike protein of SARS-CoV-2 into human cells.

Covaxin contains an inactivated (killed)SARS-CoV-2 (Strain: NIV-2020-770) which is disabled for replication. But still, the proteins are intact which are capable to trigger immunity of the host.

Chemical Ingredients:

Covishield

- L-Histidine Ethanol
- L-Histidine Hydrochloride Monohydrate
- Magnesium Chloride Hexahydrate
- Polysorbate 80*
- Sucrose
- Sodium Chloride
- Disodium Edetate Dihydrate (EDTA)
- Water for injection

Covaxin

- Aluminum Hydroxide gel
- Imidazoquinolinone # (TLR 7/8 agonist)
- 2-Phenoxyethanol
- Phosphate buffer saline

#Also known as Algel-IMDG which is an adjuvant required for Covaxin but not for Covishield

Mechanism of Immunization:

Covishield – antibodies against only a specific region of the virus is produced by this vaccine. It consists of a portion of the DNA which encodes for the spike protein (S-protein).

Why Chimpanzee Adenovirus is taken for preparing the Covishield vaccine?

It generates strong immune response.

It is not a replicating virus, hence cannot cause ongoing infection in vaccinated individuals.

It is safe for children, elderly and persons with pre-existing conditions like diabetes etc.

Well studied vaccine vector is safely used in thousands of vaccines.

Covaxin –the antibodies against many regions of the complete virus is produced by this vaccine. As this vaccine contains a full inactivated virus with having intact all its 29 proteins, the immunity provoked by it will be more comprehensive and closer to natural immunity arising out of an infection.

Alternative adjuvant "Algel-IMDG (Imidazoquinolinone)" used by Bharat Biotech can stimulates Th-1 type immunity which is also produced by mRNA/DNA vaccines.

Sputnik V in India⁶

The Gam-COVID-Vac is a two-vector vaccine.

The component which is active for both vectors is a modified (recombinant) replication-defective adenovirus of a different serotype (Serotype 26 containing $(1.0 \pm 0.5) \times 10^{11}$ gene particles for the first vaccination and serotype 5 containing $(1.0 \pm 0.5) \times 10^{11}$ particles of gene for the second

vaccination), which has been modified to include the spike protein-expressing gene of SARS-CoV-2.

Excipients are the same, both qualitatively and quantitatively, in the two components.

- Tris(hydroxymethyl)aminomethane
- Sodium chloride (salt)
- Sucrose (sugar)
- Magnesium chloride hexahydrate
- Disodium EDTA dihydrate (buffer)
- Polysorbate 80
- Ethanol 95%
- Water
- Neither adjuvants nor other ingredients or components should be included in the vaccine

ZyCov-D vaccination-A game changer⁷

1. ZyCoV-D is the world's first DNA coronavirus vaccine. This vaccine is made up of genetic material that directs human cells to produce the SARS-CoV-2 antigen.
2. Children were also involved in the experiment, hence if this vaccine got approved by the DCGI, it will be India's first vaccination for children less than the age of 18.
3. Additionally, this is the first vaccination to include three doses(0, 28,56 days regimen)

Dosage Regimen:

2 doses of Covishield has been recommended. Observation of data from the UK shows improved protection with a gap of 12 weeks between 2 doses; though currently the expert committee set up by the DCGI has recommended a gap of 4 weeks.

Covaxin is recommended to be taken in 2 doses ,each 4 weeks apart.

Efficacy:

Covishield has an average efficacy of 70% when 2 doses are administered 4 weeks apart.

An efficacy of 81% is shown by Covaxin phase-3 interim. Thus, from efficacy angle, Covaxin scores higher than Covishield with more robust and

coherent data in Indian subjects.

Vaccination in India⁹

Indian Government started the vaccination rollout on 16th January 2021 and so far around 71 crore people (as of 9th Sep) have been vaccinated with priority to healthcare and other frontline workers

Vaccines Resilient to Mutant Variants

The First –generation vaccines have a capacity to trigger an immune response which will be effective against mutant strains reported so far. SARS-CoV-2 is not highly prone to mutations, which is an advantage, said Dr Vineeta Bal, Former Staff Scientist , National Institute of Immunology, New Delhi.

HCWs	1st Dose	1,03,62,250
	2nd Dose	85,38,334
FLWs	1st Dose	1,83,34,029
	2nd Dose	1,37,98,266
Age Group 18-44 years	1st Dose	28,64,51,739
	2nd Dose	3,87,13,940
Age Group 45-59 years	1st Dose	14,03,00,422
	2nd Dose	6,05,11,083
Over 60 years	1st Dose	9,14,48,566
	2nd Dose	4,81,38,799
Total		71,65,97,428

Figure 4 : Vaccination India

Posted On: 9th September 2021 9.55 AM by PIB Delhi, Ministry of Health and Family Welfare

Who all Should Avoid Vaccination Temporarily¹⁰

Covid Vaccination to be deferred for 3 months after recovery in the following conditions:

- Persons having active symptoms of COVID – 19 infection
- COVID -19 patients already taken anti-COVID-19 monoclonal antibodies or convalescent plasma
- Acutely ill and hospitalized patients

Who all Should Take Special Precautions

We have to be cautious with persons having a history of any bleeding or coagulation disorder like:

- Clotting factor deficiency
- Coagulopathy
- Platelet disorder

Vaccination in Comorbidities

Persons with the following conditions can be vaccinated:

- Persons with a past history of COVID infection and or RT-PCR positive illness
- History of chronic diseases & morbidities (cardiac, Diabetes, neurological, pulmonary, metabolic, renal, malignancies)
- HIV, Immuno-deficiency or patients on immune-suppression due to any condition (but response to the COVID-19 vaccines in these individuals may be less).

National COVID vaccination Program

GOI will procure 75 % of vaccine provided in India

Vaccine will be given free of cost to state /UTs citizen.

Prioritization :

- HCW
- Frontline workers
- Citizen above 45 years of Age.
- Second dose due
- Citizen 18yrs &above

Private Hospitals can charge maximum Rs 150 per dose - service charges (MOH 20th June 2021)

GREY AREAS in COVID Vaccines

One year on, the light at the end of the tunnel still seems to be hazy !

Assumptions, confusion, conjectures, controversies, arguments, hopes, suspicion, presumptions, disappointments, stress, fear, – all rolled into one CORONA phenomenon.

• Age Restriction

The deaths that occurred soon after vaccination in Norway made the authorities

there advise against vaccinating people above the age of 80.

Later several countries (Germany, France, Austria, Belgium, The Netherlands, Sweden and Italy) had taken similar steps of advising against vaccinating people above 55 to 65 years with the Anglo-Swedish AstraZeneca vaccine (equivalent to our 'Covishield'), though the EU's medicine regulator gave the green light for use in adults of all ages.

The latest European nation to restrict use of the AstraZeneca vaccine to people under 55 is Spain. A grey area, indeed.

• Vaccine Hesitancy

There has been undue publicity to some of the adverse events that followed the vaccination, creating a scare among the public. Added to this has been a remarkable natural decline in the impact of the epidemic in India even before starting the vaccination programme. This situation enhanced the 'vaccine hesitancy' to that extent that, as on February 6, 2021, only 55% of the targeted 'healthcare workers' and 4.5% of 'frontline workers' in India were vaccinated. And in Tamil Nadu, only 9.6% of the 3-day target of vaccination was achieved in the first week of February 2021. Another grey area.

COVID Vaccine and Anaemia

o G6PD deficiency

The persons having G6PD deficiency, prevention of infection is important. No scientific evidence shows any contraindications to covid vaccines in G6PD.

o Aplastic Anaemia

Covid vaccination is allowed unless other contraindications.

A platelet count is less than 30K, a medical team advice is better.

National Blood Transfusion Council debars blood donation for 14-28 days after COVID vaccine

- **COVID Vaccine and Zoster**

The general advice from CDC is that no other vaccines to be given within 14 days after getting the COVID-19 vaccine.

Reactivation of VZV cause Herpes zoster that may occur spontaneously or can be triggered by any stress, trauma, fever or immunosuppression. It is well known that stress and fever are common side effects of current Covid vaccines.

- **Acyclovir Therapy and COVID-19 Vaccines**

Some people on regular Herpes (ophthalmicus) prophylaxis with acyclovir have doubts whether to go ahead with Covid Vaccination or defer the same. Expert from American Academy of Allergy, Asthma & Immunology states that such therapy would not be a reason to delay the COVID-19 vaccine dose.

- **People with Positive ANA and COVID Vaccine**

Positive ANA can be found in number of conditions like SLE, Sjogren's syndrome, Scleroderma, Rheumatoid Arthritis and can even be false positive without any illness.

COVID vaccination in all patients with positive ANA should be encouraged. If on Steroids Immunogenicity may be low. Just minimum dose of Steroids should be maintained. Extra caution is advised for SLE patients as higher incidence of hypersensitivity seen in SLE.

- **Vaccination in pregnancy (ICMR, 19th May, 2021)**

Benefits :

Studies have shown that hospital admission and severe illness may be more common in pregnant women as well as pregnant women with underlying medical conditions (compared to those not pregnant), especially those in the third trimester of pregnancy and that preterm birth is more likely (compared to pregnant women without Covid-19). Vaccination is effective in preventing Covid-19 infection in pregnancy.

Risks :

Side effects of vaccine are common. These do not affect pregnancy, but may include-Injection site reaction (sore arm).

- Fatigue
- Headache
- Muscle pain
- Fever chills and joint pain

No specific testing of the vaccine in pregnant women is done.

Pregnant & Lactating Mothers can have any Brand of Vaccine.

- **Migraine and Covid vaccine**

Headache is a common side effect of all currently approved Covid Vaccines, The leaflet insert of Covishield (AstraZeneca Oxford) lists headache among common side events which is shown in more than 1 in 10 people after vaccination. Practically incidence is far more than recorded, Unpublished reports say headache is usually seen in more than 50% people taking vaccine. Pfizer clearly admits that ~64.5% people reported headache after the jab.

The known case of migraine, are usually concerned about the headache as side effect and hence they experience it after getting the vaccine shot.

Thus covid vaccine can precipitate migraine. But mostly it is of mild intensity for few days and got relieved with usual medicines.

VIITT (Vaccine Induced Immune Thrombotic Thrombocytopenia)¹¹

Usually after 5–20 days of vaccination thrombotic phenomena occurs; thrombocytopenia is noted in all these cases. For this an early detection of thrombotic effect in those patients suspected to have VIITT is crucial. Diagnosis is based on ELISA testing and the platelet count to detect PF4-heparin antibodies. The D-dimer level more than 4.0 mg/l is suspicious. Corticosteroids, Intravenous

immunoglobulin, and anticoagulants(non heparin) are the mainstay of treatment

In Europe few patients shows Central venous Sinus Thrombosis (CVST), Splanchnic Vein thrombosis, Pulmonary embolism, DVT etc following an Astra Zeneca vaccine AZD1222. Most of the patients were women under age 55, and the fatality rate among those who develop clots is as high as 40%.

Central Venous Sinus Thrombosis usually occurs between 4 and 20 days after getting an Astra Zeneca vaccine and the symptoms may mimic as stroke or as heart attack.

Thrombotic phenomenon may be due to AZD1222 vaccine induced development of platelet-activating antibodies directed against platelet factor 4 (PF4). This prothrombotic status clinically mimics heparin-induced thrombocytopenia but showing a different serological profile.

As per European Medicines Agency (EMA)

Report dated 30 March: there had been 62 cases worldwide of cerebral venous sinus thrombosis, 44 of them in the European Economic Area, which includes the European Union, Iceland, Liechtenstein and Norway. These figure did not include all Germany's cases, however. Roughly 100 cases of unusual thrombosis out of nearly 1 crore shots of vaccine used in Europe

In Canada on 29th March the use of the Oxford-AstraZenec vaccine suspended for people below age 55 after concerns that it might be linked to rare blood clots

USA giving priority to manufacturing J&J vaccine over AstraZeneca

No issues in India- We continue to use Astra Zeneca vaccine as stated by NITI Aayog member Dr VK Paul on 23 March , "There were concerns of blood clotting in other nations. We have checked and our own research community has not found any problem. Hence Covishield for vaccination will continue in India."

Vaccination in recovered / reinfection cases

Concern is expressed about the reported cases of reinfection with mild or no symptoms, which may

be infective. The 'reinfected' cases had only mild symptoms. Breakthrough Infections are less than 0.009 & mild (CDC report).

As suggested by observations and by a 'macaque model', reinfection seems to be very rare (globally, around 10 documented cases only, out of 47 million 'recovered' cases), despite more than eight months of circulation of the virus worldwide.

The immunity offered by the natural infection probably lasts for a long term by virtue of T-cell immunity even when antibodies may not be detectable any more. This means that absence of antibodies does not mean lack of immunity or absence of evidence of previous infection.

Perhaps, the 'recovered' cases may gain more immunity even with one dose of the vaccine, going by the results of the serendipitous 'half-dose-accident' of the Oxford vaccine trial. The implications are yet to be known.

Vaccination may confer better immunity than natural infection.

CDC definition of Breakthrough Infection:

The US Center for Disease Control defines a breakthrough case as a "person who has SARS-CoV-2 antigen or RNA found from a respiratory specimen which was collected 14 days after completing the primary series of a USFDA-approved vaccine.

Why do breakthrough infections Occur?

1. No vaccine is 100% effective in all.
2. Some immunocompromised people may not develop any antibodies to vaccine.
3. Some may have been infected before the vaccination.
4. Virulent mutant strains of Virus may evade vaccine protection.

Vaccine Reinfection^{12,13}

Some Coronavirus Variant can Affects Vaccinated People upto 8 Times More Than Unvaccinated: Study From Tel Aviv University

The vaccine is accelerating the adaptive response of the virus that forms new strains which are far more infectious and potentially deadly... and that these "super strains" are emerging from "fully vaccinated subjects".

Geert Vanden Bossche, DVM, PhD is expert in a vaccine research.

Breakthrough infections¹⁴

Study of Breakthrough infections among vaccinated by ICMR in 17 states between March-june 2021.

Average days after vaccination to get infection is 39.

A) Symptoms

- Symptomatic at 70%
- Asymptomatic 30%
- Most common symptoms are fever, constitutional symptoms, sore throat and cough

B) Variant

- Delta is responsible for 85% of the cases

C) Hospitalizations

- Full vaccination reduce the hospitalizations by 91%

D) Death

- Full vaccination reduce the chances of death by 99.5%

What do we learn from data on Break through infections?

1. Breakthrough infections occur in about 5-6% HCW (health care workers) despite two doses vaccination.
2. Breakthrough infection is more prone in HCW by virtue of their job- Higher exposure, stress and work load.
3. Breakthrough infections are more prone in young HCW because of their preferential duties with higher mobility in high risk areas.
4. Health workers' data of breakthrough infections may not be applicable to society as large because differential exposure

conditions.

5. Co-morbidities may not remain a predisposing factor after vaccination as far as breakthrough infections are concerned.

VACCINE DEATHS¹⁵

First data out on a larger cohort; 5800 got infected after full vaccination out of 77 million fully vaccinated individuals. (~0.007%)

396 out of 5800, people got hospitalized (~7%)

Of those 396 folks, 74 still died.

(74 dead out of 77 million vaccinated.)

So the vaccine is 99.9999% protective against death.

Current Vaccines Advisory

All approved vaccines including Pfizer, Moderna, Covishield and Covaxin have ~100% efficacy in preventing Death due to Covid, And

- Very High efficacy against Severe COVID
- High to moderate efficacy (60%-95%) against symptomatic COVID but
- poor efficacy only against asymptomatic COVID so people should not run after efficacy data while choosing a vaccine.
- Nasal vaccines might be able to prevent even asymptomatic covid because it generates local IgA antibodies cutting chain of transmission and bringing an end to this pandemic.
- Vaccination of 10000 pregnant ladies has been done in USA without any additional side effects seen up to 3 months of follow up. Hence, Pregnant & lactating ladies can be safely vaccinated.
- People with allergy to food, drugs, latex, venom previous non covid vaccine can safely take COVID vaccine.
- Only People with severe anaphylaxis to previous covid or non covid vaccine should avoid covid vaccine.
- People who have had Covid in past must go for Covid Vaccination 3 months after recovery

- 6 month ? Data is emerging that they might need just one shot of vaccine as Robust Neutralising antibody titres and Strong T cell responses have been found in them even after single shot of vaccination.
- People who have received Plasma therapy should wait at least 3 months before taking a vaccine . Because during these four weeks the preformed antibodies transfused in external plasma will wane off and this will avoid the neutralization of virus(protein) produced by COVID vaccine.
- People with Severe disease who are admitted ICU should wait at least 4 to 10 weeks after recovery before taking any vaccine.
- People with Diabetes should go for vaccination after taking food/breakfast.
- People who are on Corticosteroids should decrease dose to less than 7.5 mg per day if possible for six weeks when taking the vaccine because higher doses act as immunosuppressive and may decease immunity development.

Updated COVID Vaccine Facts¹⁶

- Vaccination should be deferred by 3 months after clinical recovery.
- Lactation is NOT a contra – indication of the vaccine.
- No PCR/RAT screening is needed, prior to vaccination.
- COVID-19 vaccination will not cause a positive PCR or Rapid Antigen test
- If infected with COVID after first dose delay the second dose by 3 months after clinical recovery
- Blood donation can be one only after 14 days of vaccination
- Patients with other serious illness needing hospitalization or intensive care should defer vaccination by 4-8 weeks

Can I have a second dose with a different vaccine than the first one?

- While clinical trials are going on, there is not

enough data yet to recommended this combination.

FUTURE OF COVID VACCINE:

- Whether COVID-19 will join influenza as an infectious disease for which annual vaccination is required isn't yet known.
- Need to be prepared to make alterations in the existing [COVID-19] vaccines to deal with [variants] that emerge.
- Manufacturers say they're developing strategies to deal with the possibility of a variant that escapes coverage by first generation vaccines (Janssen plans to launch a phase 1 trial of aSARS-CoV-2 variants vaccine by this summer - FDA source).
- Pfizer and BioNTech begun evaluating the safety and immunogenicity of a third dose of their vaccine to see whether it would boost immunity to SARS-CoV-2 variants + discuss clinical study to evaluate a modified vaccine based on the B.1.351 (South African) variant.
- Moderna announced planning vaccine candidate based on B.1.351.
- Novavax developing a booster, a combination bivalent vaccine, to protect against variants.

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COVID 19 Vaccine

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INTRODUCTION

The world has experienced numerous pandemics till date. To name a few- influenza, cholera, plague, small pox and now the first ever pandemic caused by coronaviruses, COVID-19. After the first case was documented in Wuhan in December 2019, the World Health Organization declared this respiratory outbreak a Public Health Emergency of International Concern on 30th January 2020, and subsequently a pandemic on 11 March 2020. The culprit virus was initially recognised as novel coronavirus (n-CoV19) and later named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Previous outbreaks caused by coronaviruses, well known to history were managed to be contained. Severe Acute Respiratory Syndrome (SARS) CoV outbreak occurred in China in late 2002, had a case fatality rate of ~10 %[1,2] and Middle East Respiratory Syndrome (MERS) CoV outbreak that started in Jeddah, Saudi Arabia in late 2012[3], had a case fatality rate of ~35 % and ~2500 confirmed cases were reported until January 2020 across the globe[4] and had substantial impact on morbidity and mortality[5,6]. The current COVID-19 pandemic caused by another coronavirus, SARS-CoV-2, is continuing to be a major threat to public health and socioeconomic growth throughout the world[7,8].

The World Health Organization (WHO) and the National Institutes for Allergy and Infectious Diseases (NIAID) released a list of organisms with epidemic potential to be focussed on research and development. It is a long list viruses, bacteria, fungi and protozoa, for which efficient therapeutic options are lacking[9,10]. One among them, the coronaviruses are a large family of zoonotic viruses causing illnesses in different animals with diverse host range and tissue affinity from mild respiratory

illness to severe diseases. Of these a few from alpha and beta genera are known to infect and cause disease in humans. These include, two α -CoV (HCoV-NL63 and HCoV-229E) and five β -CoV (HCoV"OC43, HCoV-HKU1, Severe Acute Respiratory Syndrome-CoV (SARS-CoV), Middle East respiratory syndrome-CoV (MERS-CoV) and Severe acute respiratory syndrome CoV-2 (SARS-CoV-2))[11].

SARS-CoV-2 is a single stranded RNA virus classified in the order Nidovirales, family Coronaviridae, subfamily Coronavirinae and genus Betacoronavirus. It is composed of spike (S) protein, envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein, and accessory proteins. SARS-CoV-2 shares genetic similarity with SARS-CoV and has a similar entry mechanism to infect human cells[12]. It includes interaction of human angiotensin-converting enzyme 2 (ACE2) with the receptor binding domain (RBD) of S1 subunit of S protein, followed by membrane fusion mediated by S2 subunit[13]. Therefore S protein acts as a critical component for host infection. Also, neutralizing antibodies generated in COVID-19 patients were found to target epitopes within the S protein.

The genome of 29,903 nucleotides of SARS-CoV-2 which is ~50 % similar to that of MERS-CoV and ~80 % to that of SARS-CoV was sequenced and announced early in the COVID-19 pandemic in January 2020. Previous knowledge since the SARS and MERS outbreaks have significantly accelerated our current understanding of various aspects of disease entity aiding in the ongoing efforts worldwide to invent different therapies and vaccines.

We intend to give an over view and an update on the current Covid-19 scenario including vaccination in India and worldwide.

EPIDEMIOLOGY

The disease commonly causes flu-like symptoms with a mean incubation period of ~5–6 days, on the contrary to 2–11 days in SARS-CoV[14,15]. The prodromal phase may last up to 10 days and maximal virus shedding is known to occur 5–8 hrs prior to symptom initiation. The most common symptoms are fever, cough, and dyspnea, accounting for approximately 83%, 82%, and 31% of patients, respectively[16]. Most infected individuals recover, but in severe cases may progress to develop pneumonia, acute respiratory distress (ARDS), multiorgan dysfunction and death[17,15].

Globally, as of 4:18pm CEST, 16 September 2021, there have been 22,62,36,577 confirmed cases of COVID-19 and 46,54,548 deaths reported to WHO. And as of 14 September 2021, a total of 5,63,45,33,040 vaccine doses were administered. In India alone, from 3 January 2020 to 4:18pm CEST, 16 September 2021, there have been 3,33,47,325 confirmed cases of COVID-19 and 4,43,928 deaths reported to WHO. As of 13 September 2021, a total of 75,22,38,324 vaccine doses have been administered in the country. Table 1 gives the global data related to COVID-19 as per WHO.

To aid in decision making throughout the world, COVID-NMA is an international research initiative working in conjunction with the World Health Organization (WHO) providing a living mapping of COVID-19 trials and also synthesizing living evidence on various therapeutic and preventive

aspects of the disease. Several variants of concern of SARS-CoV2 have been described in literature, namely- alpha, beta, gamma, delta and epsilon. Table 2 depicts various disease characteristics in different variants.

Pathogenesis

SARS-CoV-2 has higher extent of transmission as compared to the previously reported coronavirus SARS-CoV with a high reproduction number ($R_0 = 2.2$) and the 10–20 folds greater affinity to angiotensin-converting enzyme 2 (ACE2) receptor rendering it more infectious[18,19].

Pathogenesis involves virus entry into the host cells through the receptor mediated endocytosis via ACE2 receptor, expressed in the lungs, kidney, heart, liver, testes, and intestine, and subsequent viral replication. TMPRSS2 (transmembrane protease serine 2) and clathrin protein aid in the above process [20, 21]. The subsequent upregulation of the immune system after stimulation by the virus and later failure to downregulate causing hyperinflammatory state in the body(cytokine storm) is thought to be primarily responsible for the extensive organ damage seen in severe disease[22]. It includes cardiovascular, neurological, thrombotic, hematological complications, etc[23,24].

Various pathways known to be responsible in the pathogenesis include- interleukin-6/Janus kinase/ STAT (IL-6/JAK/STAT) pathway, interferon (IFN) cell

Table 1. WHO COVID-19 global data (September 17th 2021 at 7.38.02 PM)

Name	WHO Region	Cases - cumulative total	Cases - cumulative total per 100000 population	Deaths - cumulative total	Deaths - cumulative total per 100000 population
Global		226236577	2902.5	4654548	59.71
United States of America	Americas	41229421	12455.92	659336199.19	
India	South-East Asia	33347325	2416.47	443928	32.17
Brazil	Americas	21019830	9888.92	587797	276.53
The United Kingdom	Europe	7312687	10772.01	134647	198.34
Russian Federation	Europe	7214520	4943.67	195835	134.19

Table 2. Characteristics of variants of concern.

Variant (region of prevalence)	Characteristics
Delta B.1.617.2 (India)	Increased transmissibilityModerate reduction in neutralization to post-vaccination sera
Alpha B.1.1.7 (United Kingdom)	Increased severity of disease Increased transmissibility, comparable to Delta variantMinimal reduction in neutralization
Beta B.1.351 (South Africa) Gamma P.1 (Brazil) Epsilon B.1.427 (USA)	Increased transmissibility (Beta variant)Reduced neutralization with monoclonal antibody therapies

signalling pathway, tumor necrosis factor-á-nuclear factor-kappa (TNFá-NF-ќB) pathway, toll-like receptor (TLR) pathway, T-cell receptor (TCR) pathway, JAK-STAT pathway, etc[25-30]. High levels of IL-1β, IL-6 and TNF-α are mainly associated with the severe forms of the disease. Other pro-inflammatory cytokines formed include interleukins IL-1β, IL-2R, IL-6; interferon IFN-γ; tumor necrosis factor TNF-α; chemokines (CCL-2, CCL-3, CCL-10) etc,. Some of the common laboratory parameters helpful in the detection of severe cases include, lymphopenia, erythrocyte sedimentation rate (ESR), ground-glass infiltrates, raised serum ferritin, lactate dehydrogenase (LDH), and IL-6[31]. It is also known that the abnormal RAS activation (hypotension, hypokalemia and lung injury through down-regulation of ACE2 and increased stimulation of angiotensin II receptor1) also plays a significant role in the pathogenesis deterioration in SARS-CoV-2[32].

The clinical course of COVID-19 in children can also be divided into two phases. The initial phase begins with the virus entering the respiratory tract binding to the ACE2 receptor[33]. The vascular endothelial cells, monocyte-macrophage system are also infected leading to viremic phase responsible for the initial cold and flu-like symptoms. This eliminated acute infection without causing any morbidity. Mild to moderate release of cytokines show beneficial effect on the virus infected cells. If not contained by these innate and adaptive responses, the second phase, with an exaggerated and unwanted cytokine storm ensues damaging the host cells/tissues leading to a greater morbidity and mortality[34].

COVID Vaccine

Understanding the genomic structure of the organism is a critical step for the development of new vaccine. Previous experiences and knowledge with SARS-CoV and MERS-CoV have aided rapid development of vaccine candidates in the current pandemic. By January 2020, the complete genome of SARS-CoV-2 was published. There is a strong global consensus that safe and effective COVID-19 vaccines are likely the most important approach to controlling the COVID-19 pandemic. And the World Health Organisation (WHO) has now identified 117 and 185 candidates in various stages of clinical and pre-clinical development as of 14 September 2021.

Antibodies against the SARS-CoV-2 viral spike protein have been shown to have neutralizing effects on the viral infection. Hence, current vaccines have been focussed to elicit antibodies to the spike protein. One subunit (S1) of the S protein is a receptor-binding domain (RBD) binding to host angiotensin-converting enzyme-2 (ACE2) receptor and the second subunit of the S protein (S2) mediates fusion with the cell membrane[35]. The production of these antibodies(IgM, IgG (mainly IgG1 and IgG3), and IgA classes) specific to S1 or S2 could help protect against further COVID-19 infection. Also the killer T cells (CD8+) in vaccinated individuals recognize and destroy any coronavirus-infected cell that display the spike proteins on its surface. Thus resulting in immune response in both the forms- humoral (antibody mediated) and T-cell (CD4+ and CD8+) mediated immunity.

However, immunization programs against SARS-CoV-2 require patient-friendly, cost-effective, rapidly producible vaccines that are capable of inducing

long-term immunity without requiring multiple booster doses. Although traditional vaccine types are extremely effective in preventing diseases, its production requires a large number of active viruses and takes a longer time for the development, especially if attenuation of pathogens is needed. Thus, more newer vaccine technologies, such as nucleic acid (DNA/RNA) based, subunit, and virus-like particle vaccines have been extensively studied for various diseases[36] resulting in a variety of vaccines with varied efficacies.

Types of COVID vaccines

1. Messenger-RNA (mRNA) Vaccines

mRNA vaccines utilize manufactured nucleoside-modified, single-stranded messenger RNA (mRNA) for coronavirus spike protein (S). These can either be non-amplifying or self-amplifying. The self-amplifying form has larger and longer expression of the target gene compared to its counterpart.

- 1.1. Pfizer–BioNTech Vaccine (PBV)
- 1.2. Moderna Vaccine (MV)
- 1.3. CVnCoV Vaccine of CureVac (CVV)

2. DNA vaccine; Vector-Based Vaccines

Utilizes viral vectors, either non-replicating or replicating. The most common replicating viral vectors currently in use are adenoviruses (human Ad5 and Ad26 adenoviruses and a modified chimpanzee adenovirus ChAdOx1) for carrying and delivering DNA of SARS-CoV-2 coding S-protein. On August 11, 2020, Russia was the first country to approve a vaccine against COVID-19 named "Sputnik V". Prior immunity to viral vector may reduce the efficacy. This is deemed to be avoided by Sputnik by using different adenovirus vectors for 1st and 2nd dose.

- 2.1. Oxford–AstraZeneca Vaccine (OAV; AZD 1222; Vaxzevria and Covishield)
- 2.2. Sputnik-V Vaccine (SVV; Gam-COVID-Vac)
- 2.3. Johnson and Johnson Vaccine (J&J V; JNJ-78436735)

2.4. AD5-nCoV (Convidecia) Vaccine

The biggest challenge for the nucleic acid (DNA/RNA) based vaccines is ensuring its safe and effective delivery into host cell using either viral vectors or a delivery system. Important advantage being short time required from the designing the vaccine to clinical trials.

3. Inactivated Coronavirus Vaccines

The inactivated vaccines manufactured in Biohazard safety level- III, express a wide range of viral antigens. As the variants of concern at present have mutations in the spike protein, inactivated virus vaccines can offer an advantage over the other vaccine types[37].

- 3.1. Covaxin Vaccine (COV; Bharat Biotech Vaccine, BBV152).
- 3.2. CoronaVac Vaccine (CV; Formerly PiCoVacc)
- 3.3. Sinopharm-Wuhan Vaccine (SWV)
- 3.4. Sinopharm Vaccine (SV; BBIBP-CorV)

4. Recombinant Protein Subunit Vaccines

These types of vaccines utilize whole or fragments of viral proteins packed in nanoparticles and tagged with adjuvants for enhanced immunogenicity[38]. These do not contain genetic material and are incapable of causing the disease.

- 4.1. Novavax (NVX-CoV2373) Vaccine
- 4.2. EpiVacCorona Vaccine (EVCV)
- 4.3. ZIFIVAX (ZF 2001; RBD Dimer) Vaccine
- 4.4. Corbevax (BECOV2D); a RBD protein subunit vaccine manufactured indigenously, is currently undergoing phase 2/3 trials on adults aged 18-80 years.(ref) DCGI has granted approval for conducting phase 2/3 trials in children between 5-18 years of age.

5. Virus-Like Particle (VLP) Vaccines

VLPs are synthesized viral proteins S, M, and E with or without the nucleocapsid. It is similar to a virus but lacks the infective viral genome

and originate from nucleated cells as a unit[39], explaining its safety in handling in a laboratory. The S protein facilitates the entry via the ACE2 receptor and also interact with B-cell receptors stimulating antibody production. These vaccines require adjuvants and repeated administration to enhance the immunogenicity. There are three VLP vaccines under development, none approved for use currently.

- 5.1. Medicago- The Canadian company using plant cells to produce a VLP vaccine is in its phase 2/3 clinical trials[40].
- 5.2. The ContiVir team- designed VLP vaccine at the German Max Planck Institute for Dynamics of Complex Technical Systems currently in preclinical trials[41].
- 5.3. GeoVax Atlanta- A Georgia-based company, has used MVA viral vectors (modified vaccinia Ankara, attenuated poxvirus) to express VLPs currently in preclinical trials[42].

6. Live Attenuated Vaccines

The Murdoch Children's Research Institute, Australia is working on BCG (BRACE trial), evidence and recommendations for which are awaited[43]. Three live attenuated vaccines for SARS-CoV-2 currently are in preclinical trials in India and Turkey[35]. One of these being COVI-VAC vaccine (via intranasal route) by the Serum Institute of India, working in collaboration with Codagenix, a New York based private biotech company[44]. Table 3 and 4 gives the summary information on vaccine products In clinical development, dated 14 Sept 2021 as per the WHO landscape.

In December 2020, FDA issued EUAs for two mRNA vaccines, Pfizer-BioNTech COVID-19 (BNT162b2; mRNA vaccine) and Moderna COVID-19 (mRNA-1273) for which the Advisory Committee on Immunization Practices (ACIP) issued interim recommendations to be used in persons aged e"16 years and e"18 years respectively. In May 2020 FDA expanded the EUA for Pfizer-BioNTech to include

Table 3. Number of doses, schedule and route of administration of candidates in clinical phase.

Number of doses & schedule	Candidate vaccines (no. and %)		
1 dose	17	15%	
Day 0	17		
2 doses	74	63%	
Day 0 + 14	6		
Day 0 + 21	28		
Day 0 + 28	40		
3 doses	1	1%	
Day 0 + 28 + 56	1		
TBD / No Data (ND)	25	21%	
	117		
Route of administration			
Oral	3	3%	
Injectable	99	85%	
SC	Sub cutaneous	5	4%
ID	Intra dermal	4	3%
IM	Intra muscular	90	77%
IN	Intra nasal	8	7%
TBD / No Data (ND)	15	13%	

Table 4. Candidate vaccines and various platforms in clinical phase of development.

Platform	Candidate vaccines (no. and %)	
PS	Protein subunit	42 36%
VVnr	Viral Vector (non-replicating)	17 15%
DNA	DNA	11 9%
IV	Inactivated Virus	16 14%
RNA	RNA	19 16%
VVr	Viral Vector (replicating)	2 2%
VLP	Virus Like Particle	5 4%
VVr + APC	VVr + Antigen Presenting Cell	2 2%
LAV	Live Attenuated Virus	2 2%
VVnr + APC	VVnr + Antigen Presenting Cell	1 1%
		117

adolescents aged 12–15 years. On July 23rd Moderna was approved for use in 12–17-year-old.

According to CDC interim clinical consideration COVID-19 vaccines, as of 23 August 2021, the FDA approved the licensure of COMIRNATY (COVID-19 Vaccine, mRNA), made by Pfizer for BioNTech, as a 2-dose series for prevention of COVID-19 in persons aged >16 years. The vaccine is also authorized under EUA to be administered to prevent COVID-19 in persons aged 12–15 years, and provide a third dose to the immunocompromised persons aged >12 years. In addition, FDA has authorized use under EUA to Janssen vaccine in persons aged to >18 years. It has recommended the FDA-approved Pfizer-BioNTech COVID-19 vaccine for use in persons aged >16 years.

Therefore, COVID-19 vaccination is recommended for all people aged 12 years and older in the United States for the prevention of COVID-19. However, those approved under BLA or authorized under EUA include age >12 years for Pfizer-BioNTech and >18 years for Moderna and Janssen. There is currently no FDA-approved or FDA-authorized COVID-19 vaccine for children aged <12 years. The clinical trials of COVID-19 vaccine ongoing in children <12 years are examining the vaccine doses with unequivocal efficacy and safety profile.

Vaccine administration

COVID-19 vaccines are administered intramuscularly as either a 2-dose regimen (Pfizer-BioNTech, Moderna) or single dose (Janssen). It is not

recommended to receive more than one complete primary COVID-19 vaccination. A person is considered fully vaccinated against COVID-19 >2 weeks after receipt of either the second dose in a 2-dose regimen (Pfizer-BioNTech and Moderna) or a single dose of the Janssen vaccine[45].

Indian scenario

COVAXIN (Bharat biotech): On May 12 2021, DCGI had granted permission to carry out phase 2 and 3 trials in > 2-year-old children. From June 2021, AIIMS, Delhi has started screening 2–17 year old for the same. Interim report after second dose is awaited.

ZyCov-D (Zydus): EUA received on July 1. It comprises of a plasmid DNA vaccine (CTRI/2021/01/030416) given in 3 doses. The immunogenicity data for adolescents is awaited.

Interval between mRNA COVID-19 vaccine doses

The second dose of Pfizer-BioNTech and Moderna vaccines should be administered close to the recommended interval, and not earlier, i.e., 3 weeks for Pfizer-BioNTech or 1 month for Moderna.

Pediatric vaccines present status

Evidence from Indian literature on COVID-19 suggests that the case fatality rate in children is low (~0.06 per 100,000 population) as compared to adults[46]. Also, many countries are still lagging in vaccinating health care workers and other high-risk groups with the first dose of vaccination. Therefore,

it is important to contemplate if children need prioritized vaccination campaigns ahead and/or along with the high-risk groups. However, high viral load in children and its excretion could infect parents, elderly, and other children. Therefore, if mandatory vaccination is implemented, high coverage thereby herd immunity could be achieved apart from preventing complicated forms of disease in children like Multisystem inflammatory syndrome (MIS-C) and persistent pulmonary damage subsequently.

UK's Joint Committee on Vaccination and Immunization (JCVI) has recommended vaccinating children aged 12-15 years with risk factors like severe neuro-disability (cerebral palsy, autism or epilepsy), Down's syndrome, immunocompromised status and profound/multiple learning difficulties. US is recommending all over 12 yrs to be vaccinated and planning to roll out vaccines to children as young as four by coming winter. The Hong Kong government rolled out the Pfizer vaccine to over 12 years. As of 5th Sept 2021, the status in India is as follows- ZyCoV-D, Zydus Cadila received EUA for use in 12-17 years; Covaxin, Bharat Biotech established safety in trials on children; Corbevax, Biological E granted nod for trials on kids above 5 years; Covovax, Serum Institute & Novavax conduct Phase-2/3 trials and J&J, applied for trials in children aged 2-17 years.

Correlates of protection

To develop an effective vaccine or a therapeutic, it is critical to understand the immune correlates of disease control. For mild disease, various correlates deemed to be of protective value are low lymphocyte counts, high neutrophil counts, low NK cells, presence of functional CD4 + T cells, CD8 + T cells and activated follicular helper T cells, increased plasma cells (B cells), presence of IgG/IgM/IgA and low levels of cytokines. The opposite is seen in severe forms of disease[47]. Challenge studies in humans with HCoV showed that serum and mucosal immune responses in the form of serum IgG, IgA and mucosal IgA provide possible correlates of protection from infection and disease.

How can the vaccines be produced so fast

Various factors played a crucial role in the faster production of vaccines during this pandemic. A few

to name include previous experience and research with similar diseases namely SARS and MERS, faster initiation and enrolment of large number of people into phase 3 trials[48], utilisation of already existent mRNA and adenovirus technology, monetary allocation to the places of research, increased prevalence of the disease, prioritizing COVID studies and the role of Coalition for Epidemic Preparedness Innovation(CEPI). CEPI is a global partnership between public, private, and civil organizations formed after Ebola outbreak in 2015, and works to accelerate the development of vaccines against emerging infectious diseases.

Safety of vaccines

All COVID-19 vaccine cases resulting in hospitalization or death are reported to Vaccine Adverse Effect Reporting System (VAERS). A few important adverse effects to note include the following-

Thrombosis with thrombocytopenia

Seen with AstraZeneca (Covisheild) and Janssen vaccine. Etiology being production of auto-antibodies against platelet factor 4, similar to the heparin induced thrombocytopenia. In a study, this was reported in 28 cases out of 8.7 million doses of vaccination administered[49]. Various risk factors identified were the administration of covid vaccine, the interval (5-30 days post vaccine), history of thrombosis (CVT/SVT/DVT), avoiding prophylactic antiplatelets, heparin, IVIg and direct acting oral anticoagulants.

Gullian Barre syndrome

Seen with Janssen and AstraZeneca vaccines with the incidence of 100 per 12.5 million doses and mean age being 54 years[50]. It is fortunately not reported in children. And in children with documented history of GBS, it is recommended to use non-adenovirus vector vaccines.

Myocarditis

Seen with Pfizer and Moderna vaccines (RNA vaccines) predominantly at-risk being 12-29 years of age. Incidence was noted to be 41 cases per million whereas in females of the same age as 4.2 cases per million. In a case series of 7 males between

14-19 years, patients presented with chest pain, ST elevation and raised trop I, and all responded to NSAIDs, IVIg and steroids[51]. Table 5 gives the incidence of myocarditis as per VAERS and VSD.

Therefore, the risk of myocarditis is increased with decreasing age, more common in males, after the second dose, with the median time of onset of symptoms being 3days (0-179 days) after second dose.

However as per the recommendations given by ACIP, benefits of mRNA COVID-19 vaccine clearly outweighed the risks of vaccination. There is low risk of myocarditis after vaccination, no alternatives to mRNA COVID-19 vaccines available for adolescents, higher levels of vaccination coverage may reduce community transmission and protects against development and circulation of emerging variants. It is also important for returning to educational, social, and extracurricular activities. However continued need to monitor the outcomes of myocarditis post COVID-19 vaccination is essential. Recommendations are depicted in the table

6.

Maternal and fetal risks

As per the literature available symptomatic maternal COVID-19 is associated with a two to three times greater risk of preterm birth and the risk of stillbirth is approximately doubled with SARS-CoV-2 infection[52].

To address various aspects of immunity in pregnant women, there is ongoing research on COVID-19 vaccination in pregnancy. A few of them include a randomised controlled trial funded by Pfizer[53] being conducted worldwide; The HORIZON1 study planned by Janssen[54], and PregCOV-19LSR pragmatic trial[55] where different vaccines on different schedules are being tried aiming to identify the most effective schedule in order to protect pregnant women, as well as to assess whether improved immunity is conferred via breast milk. Data from the Developmental and Reproductive Toxicity (DART) animal-model studies for the COVID 19 vaccines by Pfizer-BioNtech, Moderna, and

Table 5. Incidence of myocarditis according to VAERS and VSD.

	Male (per 1million)	Female (per 1million)
VAERS		
Vaccine adverse effect reporting system	12-17 years: 66.7 18-24 years: 56.3	12-29 years: 4.2 >30 years: 1 25-29 years: 20.4
VSD	12-39 years: 32	12-39 years: 4.7
Vaccine safety datalink		

Table 6. Various scenarios and their vaccine recommendations in relation to myocarditis

Scenario	Recommendation
Pericarditis prior to COVID 19 vaccination	Any FDA-authorized COVID-19 vaccine
Pericarditis after first dose of an mRNA COVID-19 vaccine	Proceed with a second dose of mRNA COVID-19 vaccine after resolution of symptoms.
Myocarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine if recovered
Myocarditis after 1st dose of an mRNA COVID-19 vaccine	Defer second dose of mRNA COVID-19 vaccine until more information is known from studies. However, if heart has recovered, could consider proceeding with second dose under certain circumstances. The clinical team need to discuss with patient and guardian.

Janssen (Johnson & Johnson) have not demonstrated any adverse safety profile in pregnancy.

As per the recommendations given by RCOG in June 2021, pregnant women should be offered the mRNA vaccines (Pfizer-BioNTech or Moderna). In case of completed first dose of Oxford-AstraZeneca vaccine, they should complete the course with the same. Vaccine can be given at any time in pregnancy. However, in low-risk situations it can be deferred until 12 weeks POG. But if there is higher chance of contracting the infection/ severe illness, vaccine should be given as early as 1st trimester. Pregnant women are more likely to become seriously unwell and have a higher risk of prematurity, if they develop COVID-19 in their third trimester. Therefore, vaccination is advised to be completed before the third trimester. Table 7 depicts recommendations given by various national and international bodies.

Efficacy and effectiveness of vaccines

The phase 3 trials of the four currently approved vaccines shows the following efficacies: the Pfizer-BioNTech vaccine- 95% (95% CI 90.0–97.9%) against symptomatic COVID-19,[56] the Oxford-AstraZeneca vaccine- 66.7% (95%CI 57.4–74.0%) against symptomatic COVID-19[57], the Moderna vaccine- 94.1% (95% CI 89.3–96.8%),[58] and the Janssen vaccine- 66.1% (95% CI 55.0–74.8%). It has been also confirmed that one dose of the Pfizer-BioNTech or Oxford- AstraZeneca vaccines confers about 60% protection against symptomatic COVID-19[59]. Table 8 depicts the efficacy, cost, number of countries approved, etc mentioned in *Ann Intern Med 2021*[60].

Tables 9, 10, 11 depicts vaccine effectiveness against SARS-CoV infection, symptomatic COVID-19 and against various variants of concern in different parts of the world.

Table 7. Recommendation of COVID vaccine in pregnancy and lactation.

Body	Recommendation
World Health Organization	WHO does not recommend discontinuing breastfeeding after vaccination.
International Federation of Gynecology and Obstetrics	Supports offering COVID-19 vaccination to pregnant and breastfeeding women.
Federation of Obstetric and Gynecological Societies of India	COVID-19 vaccine should be extended to pregnant and lactating women. The benefits of vaccinating pregnant and lactating women outweighs remote risks of vaccination.
American College of Obstetricians & Gynecologists	No difference between lactating and non-lactating mothers for COVID-19 vaccines.
Indian Academy of Pediatrics	Strongly recommends the administration of COVID-19 vaccines to all breastfeeding women

Table 8. Various vaccines approved/EUA- cost vs. efficacy.

Vaccine	Efficacy	Cost/dose	No. of doses given	No. of countries approved
COVAXIN(killed)	81%	1480	3,61,35,097	9
COVISHIELD(viral vector)	77%	780	28,00,00,000	45
SPUTNIK V(viral vector)	91%	995		70
Janssen (Viral vector)	72%	\$10	25,00,00,000	56
Pfizer/BioNTech (RNA)	95%	\$19	~30,00,00,000	97
Moderna (RNA)	93%	\$32	34,20,00,000	22

Table 9. Vaccine effectiveness(VE) against SARS-CoV2 infection in health care personnel as per CDC.

Country	Vaccine	Fully vaccinated VE
US	Pfizer	97%
US	Moderna	99%
US	Pfizer or Moderna	90%
US	Pfizer	96%
UK	Pfizer or AstraZeneca	90%
UK	Pfizer	86%
UK	Pfizer or AstraZeneca	92%
Italy	Pfizer	95%
Denmark	Pfizer	90%

Table 10. VE against symptomatic COVID-19 in health care personnel as per CDC.

Country	Vaccine	Fully vaccinated VE
US	Pfizer or Moderna	94%
US	Pfizer	87%
Israel	Pfizer	97%
Israel	Pfizer	90%

Table 11. VE against variants of concern as per CDC.

Country	Vaccine	Strain	Fully vaccinated VE
Israel, Europe, UK	Pfizer	Alpha	>85%
Canada	mRNA	Alpha, Gamma	79%
Canada	mRNA	Beta, Gamma	88%
Qatar	Pfizer	Alpha	90%
Qatar	Pfizer	Beta	75%
South Africa	Janssen	Beta	52%

Herd immunity

Herd immunity occurs when a significant portion of a community becomes immune to a disease, either by infection or vaccination, thereby reducing the spread of disease. As a result, the entire community becomes protected and not just those who are immune. The percentage of a community that needs to be immune in order to achieve herd immunity depends upon the contagiousness of the disease. The more contagious a disease is, the greater the proportion of the population that needs to be immune to the disease to stop its spread.

A percentage of the community must be capable of getting a disease in order for it to spread, called the threshold proportion. If the proportion of the community that is immune to the disease is greater

than this threshold, the spread of the disease gradually declines. This is known as the herd immunity threshold. Unlike the natural infection method, vaccines create immunity without causing illness or complications. Herd immunity makes it possible to protect the population from a disease, including those who can't be vaccinated, such as newborns or immunocompromised individuals.

Impact of vaccine on recurrence of the infection and disease

Early high antibody titres are correlated with increased disease severity as noted in both SARS[61] and COVID-19[62,63]. Although vaccines are found to be effective in preventing COVID-19, it is rightly said that we need to be prepared for further mutations in SARS-CoV-2 and seasonal recurrences as seen in influenza. Any currently FDA-approved

or FDA-authorized COVID-19 vaccine can be used when indicated and ACIP does not recommend a preference of one over the other.

Duration of immunity

To date, antibody persistence demonstrated for up to 8 months after COVID-19 infection and 6 months after the 2nd mRNA vaccine dose[64,65]. Data from the booster studies on Moderna and Pfizer is awaited.

Antibody dependent enhancement (ADE)

In the current pandemic, specialists have suggested that immune responses against SARS-CoV-2 could lead to antibody-dependent enhancement (ADE)[66], a phenomenon well known in flavivirus and some feline coronaviruses. SARS-CoV and SARS-CoV-2 have shown not to cause this effect in humans[67]. However, a possible case of ADE was observed in a patient with a second SARS-CoV-2 infection[68]. Also if ADE becomes significant in future, the nucleic acid vaccines can provide improvisation in available candidate vaccines, by genetically modifying or excluding the sites of the genome responsible for causing ADE[69].

Risk of waning immunity

Duration of antibody protection after primary vaccination is variable. A few of the several factors responsible for the waning of immunity are time since vaccination, age, nutrition and medical condition. Khouri et al proposed a model for prediction of duration of immunity based on the initial efficacy of the vaccine[70]. Vaccine starting with initial efficacy of 95% expected to maintain high efficacy (77%) after 250 days and vaccine starting with initial efficacy of 70% may drop to 33% after 250 days.

Third dose in Immunosuppressed

A study on solid organ transplant recipients (n=30) who had suboptimal response to standard vaccination (57% received Pfizer, 43% received Moderna), 24(80%) had negative antibody titers and 6 (20%) low-positive. When 3rd dose was given around 67 days after 2nd dose: Janssen (n=15), Moderna (n=9), Pfizer (n=6), 14 (47%) responded, including all low-positives; 16 (53%) remained

negative[71]. A trial on 3rd dose of Moderna vaccine in transplant recipients is yet to be published.

Use of digital resources to increase vaccine uptake

Several health interventions are being taken up by the authorities. Public Health and Social Measures (PHSM) are steps taken by countries, territories and areas that enforce rules or guidelines to limit the spread of COVID-19. PHSM severity index is based on an average of six indicators including adaptation or closure of schools, adaptation or closure of businesses, restrictions on public and private gatherings, restrictions on domestic movement, public transport and stay at home orders and international travel restrictions (including quarantine and testing). It can support and inform the development and check compliance of policy at country and regional levels.

As the first ever pandemic in the era of universal smartphone and technological awareness, apart from the ongoing PHSM measures, digital application in India (Aarogya setu and Cowin app) and worldwide has come a long way since inception. A few of several applications include identifying the disease trends and containment/ high risk zones within different cities[72], locating and tracing of vaccination centres depending upon the area of residence, generating certificate following vaccination, etc.,

Future of vaccines

It is worth mentioning that in spite of mutations noted in SARS-CoV-2 it has not been significant enough to render the current vaccines non-productive[73].

Coadministration of vaccines

AAP supports co-administration of routine childhood and adolescent immunizations with COVID-19 vaccines for children and adolescents who are due for immunizations and at increased risk from vaccine-preventable diseases. Since the Pfizer BioNTech COVID-19 vaccine is considered inactivated, the safety and efficacy are expected to be similar to other inactive vaccines that are co-administered along with. According to AAP, there are no safety or efficacy issues expected with

coadministration of Pfizer BioNTech vaccine with live attenuated vaccines as well.

Vaccine switch

A number of people in Europe had received the initial dose of AstraZeneca, later found to have risk of clotting disorder considered a switch to another vaccine. This was also done at places where supplies of vaccine were limited. For instance, Leif Erik Sander and colleagues at the Charité University Hospital, Berlin, gave the two vaccines (10 to 12 weeks apart) AstraZeneca followed by BioNTech to a cohort of health care workers. It was noted that the levels of antibodies were comparable to a control group that received two doses of Pfizer-BioNTech at the standard 3-week interval and no increase in side effects[74].

In another Spanish study, 448 people received a dose of the Pfizer-BioNTech vaccine 8 weeks after an initial AstraZeneca dose showed lesser side effects and adequate antibody response 2 weeks after the second dose. All 129 blood samples tested could neutralize the SARSCoV-2 spike proteins[75]. Although a multicentre(UK), participant-blinded, randomised heterologous COVID-19 vaccination study with AstraZeneca and BioNTech vaccines showed greater immunogenicity with heterologous vaccine administration than the homologous counterparts, the switch between Covaxin and Covishield is currently not recommended. Studies with large groups showing similar response is awaited for such a recommendation.

The National Institutes of Health has started a Phase 1/2 clinical trial in which volunteers (adults) who have been fully vaccinated against COVID-19 would receive booster doses of different COVID-19 vaccines (BioNTech and Janssen) to determine the safety and efficacy of mixed boosted regimens[76].

Various novel types and combinations of vaccines for COVID-19 are being tried. Apart from several studies ongoing, adequate surveillance and monitoring for the origin of high-risk variants of SARS-CoV-2 is crucial. Hoping more such innovative vaccine strategies would be capable of handling future variants of concern, opening new pathways in the prevention of COVID-19.

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Evidence that vaccine protection against severe disease and death does not decrease with time.



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Summary

1. Vaccination prevents deaths. The ability of vaccines to prevent deaths has not diminished until now. Observational studies on vaccine effectiveness are prone to error from multiple confounding factors including the rise in natural immunity due to infections occurring among the unvaccinated population. This leads to a reduction in difference in event rates between the two groups, that could be misinterpreted as reduced vaccine effectiveness.
2. The ability of vaccines to prevent infection substantially diminishes within a few months. This correlates with a natural drop in neutralising antibody titres, and is often loosely referred to as waning of immunity. This should not be confused for reduction in protection against severe disease or death. Rise in infections could also be the result of lowering of guard and increased social mixing in the setting of the highly transmissible delta variant.
3. Observations worldwide have shown that even high levels of vaccination coverage are ineffective in preventing subsequent waves. However during the subsequent wave, mortality rate among the fully vaccinated is much lower than the observed rate in the unvaccinated population.
4. Most of the documented cases during such a surge occur among the unvaccinated segment of the population.
5. At least a three-fold reduction in overall risk of COVID-19 death has been consistently observed across continents, as a result of

vaccination. The extent of risk reduction could vary between age groups and between studies.

6. Emerging evidence from large studies from Israel on booster doses show a 5-fold reduction in infection rate in the first two months in the 3 dose group. A proportionate reduction in deaths also was observed. The expected duration of this protection is not known. However, when compared to the 2 dose group, there was no reduction in progression to hospitalisation, severe disease or death among those individuals who developed symptomatic breakthrough infection after 3 doses.
7. Priority must be given to providing two doses of vaccines to adults who are not yet vaccinated, and at least one dose of vaccine to those who have had prior natural infection. High vaccination coverage alone does not eliminate the possibility of future waves. Non-pharmaceutical interventions such as masking, improving room ventilation, and avoiding social gatherings are equally important pillars of control of the pandemic.

Introduction:

Even though vaccines are known to be effective at preventing deaths from COVID-19, there has been a recent concern of 'waning of effectiveness'.

An important distinction is necessary here; waning of protection from infection by the virus is different from waning of protection from severe disease and death. Unlike measles, COVID-19 vaccines do not provide sterilising immunity. In other words, within a few months of receiving the second dose, breakthrough infections are common, the vast

majority of which are asymptomatic or mild. This is often referred to as waning of immune protection.

Breakthrough infections are observed particularly when vaccinated individuals engage in social mingling without masks, in the setting of the highly transmissible delta variant.

Fortunately, this decrease in protection so far has been limited to infections and not severe disease and death.

This article examines the topic of waning immunity, primarily focusing on prevention of deaths.

A few recent publications are discussed in detail below, in order to get a global perspective. This article is based on data available at this time. As the science around COVID-19 is rapidly evolving, continued observations are necessary to detect any change in mortality patterns.

1. Study from Oregon, US on the monthly incidence rates of breakthrough deaths among 2.6 million vaccinated individuals

The following calculations are based on month-wise covid mortality data published by Oregon state, US till September 2021. (Table 1)

The table shows 1) the total number of deaths, and 2) the percentage or proportion of deaths, among fully vaccinated people in each month.

Proportion of breakthrough deaths is defined as follows:

If there are 100 deaths in the population in a month, how many were among the vaccinated?

Analysis of the data from the table above:

There was a COVID-19 surge in the US since August 2021, with high transmission and caseload in September, as illustrated in the graphs below.

As expected, the total number of deaths also increased in September.

However, there was no change in percentage (proportion) of vaccine breakthrough deaths between July (low caseload) & September (high caseload) in Oregon, US.

As the percentage of vaccination coverage in a population increases, there will be an increase in the percentage of breakthrough infections as well. While looking at all COVID deaths, the percentage of deaths contributed by the fully vaccinated will also go up, in comparison with earlier months when only few had been vaccinated.

However, the number of people who die as a result of breakthrough infections will be substantially lower compared to a time when the same population was unvaccinated.

To illustrate this with an example: in a hypothetical town where the population was 100% vaccinated a

Table 1 : COVID-19 deaths by month, by breakthrough case status

Month	Total COVID-19 deaths	Vaccine breakthrough deaths	Percent vaccine breakthrough deaths
March 2021	118	4	3.4
April 2021	105	6	5.7
May 2021	183	15	8.2
June 2021	94	13	13.8
July 2021	81	16	19.8
August 2021	418	96	23.0
September 2021	633	126	19.9

month ago, if there are 10 deaths from COVID-19 in a month, the *proportion* of deaths from breakthrough infection will also be 100%. That doesn't necessarily mean "vaccination failure". Because, if that same population had been unvaccinated, perhaps the number of deaths could have been three times higher at 30.

The above table shows that the percentage (proportion) of vaccinated deaths has remained constant in those 3 months, in spite of the fact that vaccination coverage increased from 23% to 57% during that period.

This implies that the protective effect of vaccination against severe disease is not waning, and may in fact have increased. This is known to spontaneously occur from affinity maturation, somatic hypermutation and antibody class switch in memory B cells, during the months following vaccination (6,7), even though the total antibody titres fall naturally to reach a low and steady baseline production.

In other words, vaccines continue to be effective in preventing deaths - even after several months have passed.

(If vaccines became ineffective in preventing severe disease and death, then a much higher percentage of breakthrough deaths should have occurred in September, when there was high caseload)

Next, the effect of vaccination on deaths was examined in the months of May and September. It was found that there was no difference in the *reduction in death rate* from vaccination. The conversion factor (ratio) for both months was identical at 2.8.

What is the conversion factor?

This ratio or "conversion factor" is derived as following:

percentage of full vaccination (one month prior)

percentage of breakthrough infections among all reported deaths in a given month.

For example, in the month of May, 8.2% of all deaths were from breakthrough infections. Correspondingly, full vaccination coverage was 23%; that was on 14th of April. The reason for choosing 14 April

in this case was because severe outcomes at any given time reflect vaccination rates that prevailed at least one month prior.

The ratio between the two is 2.8. In other words, deaths were 2.8 times more likely to occur in the unvaccinated segment when compared to the vaccinated segment. In real world observational studies, this ratio provides an estimate of how well vaccination protects against the end point of death.

The following example illustrates why this ratio is important.

We know that 23% of the population was fully vaccinated on 14th of April.

Hypothetically, if this vaccine was *not effective* in preventing deaths, we will expect the same percentage, that is 23% of all subsequent deaths to belong to the fully vaccinated segment. (During the month of May). Instead of 23%, only 8.2% of deaths in the month of May occurred in the vaccinated segment.

In other words, the lower the observed percentage of deaths in the vaccinated segment, the higher the ratio, and the greater the protection achieved. 2.8 is a very good ratio, which validates the role of vaccination in reducing deaths from COVID-19 in the real world. Comparable ratios have been calculated from data elsewhere.

In reality, this ratio is likely to be an underestimate of vaccine protection, because older people with comorbidities, i.e. those at greater risk of dying - are more likely to have received the vaccine. In contrast, unvaccinated individuals are more likely to be younger and healthier. This means that the baseline risk of dying in the vaccine group is already higher than the unvaccinated group. Therefore, any reduction in death rate noted in the vaccinated group implies that the true level of vaccine protection is even higher than observed.

In summary, if a person is unvaccinated, they are approximately three times more likely to die than if the person was fully vaccinated (2 dose mRNA or 1 dose J&J were used in this population).

Similarly, for the month of September, the percentage of deaths due to breakthrough infection was 20%.

The corresponding full vaccination coverage was 57%. Thus, the conversion factor or ratio was identical at 2.8.

The difference between absolute numbers and percentages



An easy way to explain the difference between total number and percentage is to imagine a white balloon with a large red dot on it. Before inflating the balloon, it can be seen that the red dot covers 10% of the balloon surface area, but the dot is obviously small.

Once the balloon is blown up to full size, the area of the dot becomes much larger - but the proportion (10%) in relation to the total area remains the same. In other words, even though the dot has become larger, the ratio between the red area and the white area remains the same. This example illustrates the difference between proportion and absolute numbers.

Applying this example to deaths in COVID-19, even though the total number of deaths has increased with the surge in September, the *proportion* of deaths among the fully vaccinated has not increased.

This means that vaccines are continuing to protect individuals from dying, regardless of the prevailing infection rate in the region.

Note: deaths that were reported in September will largely be determined by the vaccination status in August or earlier (due to lag in several factors). Hence it is too early for any protective effect from boosters to show in this table.

2. CDC Veterans study, US: Vaccination protection for severe disease does not decline

A CDC MMW report on US veterans showed that there was no difference in outcomes between people who were vaccinated earlier, compared to later (2). The study found that vaccine-induced protection against hospitalisation from severe COVID-19 was the same in August as it was in February. This shows that vaccine effectiveness in preventing hospitalisation did not drop with time.

Vaccine effectiveness in preventing hospitalization was 80% among e"65 years compared with 95% among 18–64 yrs.

COVID-19 cases per 100,000 per week, by vaccination status

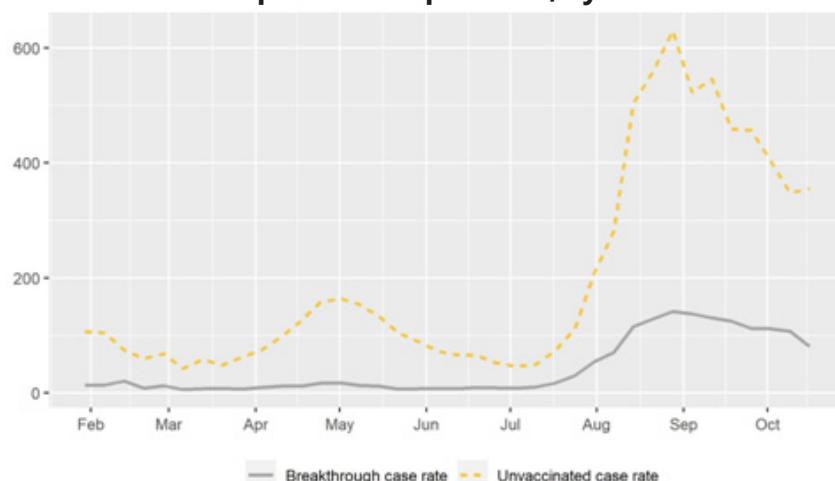


Figure 1 shows that most of the cases during a surge occur among the unvaccinated.

COVID 19 breakthrough cases, hospitalization and deaths, by week

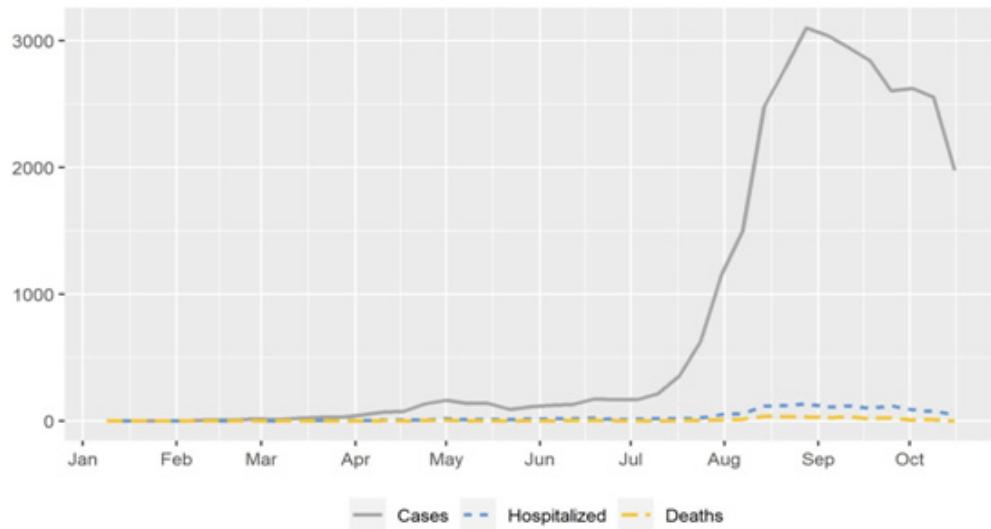


Figure 2 shows that even though more breakthrough infections occur during a surge, the vast majority are mild and do not result in hospitalisation or death.

This is not to be interpreted as a "decline in effectiveness with time" but rather as a difference in baseline risk.

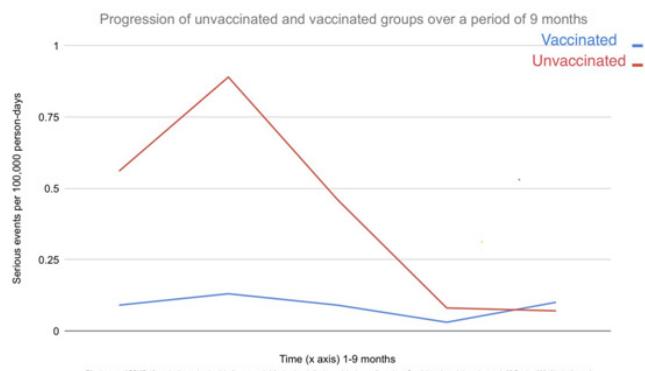
3. Experts consensus about booster doses

A recent consensus article published in *The Lancet* by domain experts from around the world concluded that there was no decline in protection from severe disease since the launch of vaccination (8).

4. Long term follow up study from Sweden comparing vaccinated and unvaccinated people

A study from Sweden of over 1.6 million people reported an apparent decline in vaccine effectiveness against both infection as well as severe disease over a 6 month period (10). However, a closer look at the data revealed that it was actually due to a gradual *increase* in the immune protection that occurred in the *unvaccinated group* (presumably due to natural infection) rather than a decrease in the vaccinated group.

As the conventional method for measuring effectiveness is to compare infection rates between vaccinated and unvaccinated groups, the ratio was misinterpreted by authors as a decline in effectiveness.



Graph comparing serious event rates among vaccinated (blue) and unvaccinated (red) individuals in Sweden. During follow-up past 6 months, there was no increase in serious events in the vaccine group. At the same time, the rates in the unvaccinated group progressively decrease to equal the vaccinated.

5. Israel study comparing 2 dose and 3 dose vaccinated individuals

A large study from Israel published in *The Lancet* on October 28 compared 728,321 patients who took 3rd dose with those who had received 2 doses earlier. The authors reported that infection rates following the third dose was lower by 5.4 fold, compared to the two dose vaccinated group (9).

However, among those who developed symptomatic infection, the risk of progression

to hospitalisation, severe disease and death was almost identical in the two dose and three dose groups. This indicates that the added benefit of a third dose is essentially restricted to a reduction in the total number of infections, and its natural consequences.

It is worth remembering that COVID-19 is a biphasic illness. The first step is the infection in the nose and throat, and the second step is severe disease, resulting from organ damage. The first step is believed to be prevented by high initial levels of neutralising antibodies after vaccination, while the second step is prevented by the concerted action of memory cells and T-cells.

High levels of circulating neutralising antibodies immediately following the second or third dose prevent infections. However, high antibody levels cannot be maintained for longer than a few months.

In contrast, the protection offered by T cells and memory cells is expected to remain intact for many years. There is no evidence that a 3rd dose will further enhance this segment of the immune system.

To put this in perspective, prevention of severe disease by two doses of vaccine essentially works like a helmet for a two wheeler rider. It protects the individual from dying in case of a road accident. In this case, the road accident is a metaphor for infection. All accidents do not cause deaths, but those who wear a helmet are less likely to die if an accident occurred. The helmet by itself does not prevent road accidents.

Building further on the helmet metaphor, the third dose in the Israel study effectively worked somewhat like a strict temporary traffic curfew - where traffic rules are so strictly enforced that it *reduced the total number of accidents (infections)* by 5.4 fold. However, it must be noted that this extra step does not change the *original protection level from death* offered by the helmet.

In other words, the third dose was not a

"better helmet" or a "replacement of a damaged helmet". Thus, if the person was involved in an accident, the chance of death remained the same as before.

If the 3rd dose actually "boosted" cell-mediated immunity, fewer people (smaller percentage than the two dose group) would have died after acquiring symptomatic infection. This unfortunately was not the case. The percentage of severe outcomes following symptomatic infection remained the same in both groups.

At the same time, since the *total number of infections decreased*, the *total number of deaths* was proportionately reduced as a result of this intervention.

However, as the antibody spike that follows a booster dose is short lived, duration of this protection is not expected to be long.

On the other hand, T-cell immunity as well as memory cells of T and B categories, that develop after the second dose, are expected to last for several years. These specialised immune cells are believed to play the major part in prevention of severe disease and death. This is maximised following the second dose.

Thus, there is no evidence at the time of this writing, that symptomatic infections that occur among those who received booster doses are any less likely to progress to severe disease or death.

The role of a booster dose is a subject of divided opinion, and knowledge is still evolving. The durability of protection from infection is unknown. It is generally agreed that three doses are required for immunocompromised individuals to mount an immune response. A 3rd dose could also be considered in a vulnerable individual who is by default at high risk of exposure to virus, to temporarily minimise the chance of picking up an infection. Data are insufficient at this time to universally recommend booster doses for healthy adults.

Non-pharmaceutical interventions are also effective at minimising the risk of picking up an infection, and must be continued regardless.

Age-associated gradient in COVID-19 mortality

This is another important concept that needs to be understood in the context of vaccination across age groups. It is well-known that the mortality of COVID-19 exponentially increases in older adult age groups.

To illustrate this with an example, a 70-year-old person with COVID-19 is 220 times more likely to die than a 20-year-old with Covid 19. Even though vaccination reduces the risk in all adult age groups, this age-related gradient (difference) still remains among all vaccinated adults. In other words, a vaccinated adult at 80 is still more likely to die from Covid 19 than a vaccinated adult at 20.

6. Public Health England data comparing age related mortality among vaccinated and unvaccinated individuals

Analysis of mortality data published by Public Health England showed that a fully vaccinated person in his/her 70's is 92 times more likely to die than a fully vaccinated 18-29 year old (3).

From this series, it was possible to estimate the age related risk reduction for vaccinated individuals. It was evident that the greatest reduction occurred in the sixth decade that was between the ages of 50 and 60. The lowest reduction occurred in the oldest age group.

How many fold reduction in death risk can be expected by vaccination in each age group?

Analysis of data published by Public Health England (3) shows the following:

- 3.4 fold reduction in 80+ age group
- 5.7 fold in 8th decade (70-79)
- 6.2 fold in 7th (60-69)
- 9.7 in 6th (50-59)
- 7.7 in 5th (40-49)

Multiple series have shown that the average reduction in deaths from vaccination in an adult population will be approximately three-fold.

7. Study from South Africa comparing death rates among vaccinated and unvaccinated individuals

A study from South Africa had shown a 3.3 fold reduction in death rate among the vaccinated, compared to unvaccinated (4). Risk of death from Covid-19 was 3.3 times higher among unvaccinated (1 in 480) vs. vaccinated (1 in 1490) healthcare workers. In that series, only 1.7% of 292 deaths and 4% of 729 hospitalisations among >60 years occurred among the fully vaccinated.

8. Audit of deaths, Ernakulam, India

An Audit of 281 Covid deaths in Ernakulam, India showed that 98.2% of the deaths occurred among those who had not been fully vaccinated (5). Only 1.8% of deaths were among people who were fully vaccinated. The prevailing vaccination coverage of the adult population at the time of the audit was 68% (1 dose) and 24% (2 doses).

Even though an audit is not a measure of vaccine effectiveness, the observed death rate among the fully vaccinated was 92.5% lower than the expected death rate. Long term studies on durability of protection by vaccines in preventing deaths are not yet available from India.

Limitations

Estimation of mortality rate in the setting of the pandemic comes primarily from real-world observational studies, because randomised controlled trials are no longer possible with widespread vaccination. Observational studies comparing groups of people are prone to bias from multiple confounders such as behavioural traits, unquantified immunity from natural infection, differing baseline demography and risk profile, variation in willingness to undergo testing and data reporting.

Methodology problems

The methodology of assessing real world effectiveness of vaccines is increasingly questionable. While doing the first vaccine trials in 2020, when immunity from prior natural infection was rare, it was acceptable to compare event rates in the vaccinated group to a placebo group.

However, in late 2021, where most of the world has suffered multiple waves of the pandemic, it is no longer possible to compare event rates in two groups of patients one of whom are vaccinated and the other unvaccinated.

The reason is that as time progresses, people in the unvaccinated group pick up asymptomatic and symptomatic natural infections, developing immunity in the process. Almost like a parallel vaccination process, this reduces the subsequent event rates in the unvaccinated group, as seen in the Swedish study by Nordstrom et al. This was erroneously interpreted as a decline in vaccine effectiveness against severe disease. In reality, the event rate in the vaccinated group had not increased even after 8 months - as shown in the graph above.

The reason for this error is that, even if the event rate among the vaccinated group does not increase, when a comparison is done a few months later, the *difference* between the two groups is substantially smaller. If the old method of comparison is followed, this gets misinterpreted as a decline in vaccine effectiveness, while in reality this represents an *increase* in the natural immunity among the unvaccinated group.

This can be compared to an express train moving at a steady speed, falsely appearing to be slowing down, when a slow train in a parallel track starts picking up speed.

Therefore vaccine effectiveness must be compared to a baseline event rate and probability of disease progression, rather than continue to compare with people who have chosen not to vaccinate themselves.

As more data is collected, it is important to look for emerging patterns in multiple studies from several regions.

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INTRODUCTION:

Corona virus disease (COVID-19) has impacted us in an unprecedented way, every aspect of life is affected and the way we practice Medicine has changed. Practice of every speciality during the pandemic is challenging but the challenges in Obstetrics are even more significant as it involves the care of the mother and the fetus and also it is continuous care for a prolonged period of time. More data has emerged now about maternal and fetal outcomes than it was during first wave and it has demonstrated that there were more adverse perinatal outcomes during the second wave which was contrary to what happened during first wave.

VIROLOGY AND EPIDEMIOLOGY:

The SARS-COV-2 is an RNA virus. Over a period of time there have been variants of concern and in India in December 2020 the Delta variant of B.1.617.2 lineage was reported which has more transmissibility, increased severity and associated hospitalisation. During the second wave there were more number of symptomatic patients, hospitalisations¹ and increased mortality and this happened among pregnant women also. The main mode of transmission is person to person. By mid-September over 33million cases have been reported in India with nearly 4.45 lakhs deaths.²

CLINICAL FEATURES:

Most pregnant women are asymptomatic though the proportion of women who are asymptomatic varies among the studies³. Cough and cold are common symptoms.⁴ Aches and pain, sore throat, fever, breathlessness and anosmia are also present in many women. Some women experience gastrointestinal symptoms. Since some of these symptoms can present in normal pregnancy also,

one has to remember this fact while evaluating women without fever.

CLASSIFICATION OF DISEASE SEVERITY:

This is the same as in non-pregnant patients

- *Asymptomatic infection:* Positive test but no symptoms
- *Mild illness:* Signs and symptoms without dyspnoea or abnormal chest imaging
- *Moderate illness:* Clinical assessment or imaging suggests lower respiratory involvement with $\text{SPO}_2 > 94\%$
- *Severe illness:* Respiratory rate $> 30/\text{min}$, $\text{SPO}_2 < 94\%$, $\text{PaO}_2/\text{FiO}_2 < 300$, lung infiltrates $> 50\%$
- *Critical illness:* Respiratory failure, shock and/or multiple organ system failure.³

DISEASE COURSE IN PREGNANCY:

Maternal course:

There is no documented increased susceptibility or increased risk of infection because of pregnancy but in those women who become symptomatic there is rapid deterioration, need for admission to ICU and mechanical ventilation which was revealed in a data analysis midway through the first wave by CDC.⁵ Though this was the pattern during the first wave, in the second wave there was an increase in mortality also when compared to women who were not pregnant in the same age group. Historically in viral respiratory illnesses complicating pregnancy, because of the altered immune response and the already stressed cardiorespiratory systems there is poor maternal-fetal outcome. Though this was not witnessed in the first wave the case fatality rate (CFR)

(0.7 vs 5.7) and the maternal mortality ratio (10.2 vs 83.3) clearly showed an increase in the 2nd wave as compared to the 1st wave in India.⁶ The reason for this is not clear but it could be because of the new variant and also because of the fact that the antenatal women were not vaccinated when the second wave started. Risk for severe disease could be infection in 3rd trimester, advanced maternal age, obesity, comorbidities like diabetes, hypertension, chronic respiratory conditions, organ transplant recipients, those on immunosuppressant medications, chronic kidney disease, cardiac disease and certain ethnic groups. The complications which arise are similar to those which happen in non-pregnant state .There are some studies which show that the thrombotic complications are more during pregnancy. In one meta-analysis of observational studies the odds of developing pre-eclampsia and related complications were found to be higher.⁷

Fetal outcome:

There is no evidence to suggest increased risk of miscarriage.^{1,3} There is an increase in preterm birth and delivery by caesarean section in many studies. Though there are some reports of congenital infection, it is uncommon.^{1,3} No increased risk for congenital anomalies has been documented. Though data on still birth directly due to the infection is not clear there can be an increase in still birth due to disruption of access to maternal care in resource poor settings.⁸ There is no increase in neonatal death in babies born of mothers with infection.

DIAGNOSIS:

Diagnosis is by detection of SARS-CoV-2 RNA by nucleic acid amplification tests (NAAT), commonly by reverse transcriptase polymerase chain reaction (RT-PCR)³ from nasopharyngeal specimens. Positive test usually confirms the diagnosis and sensitivity of RT PCR is about 65%. Newer assays have improved sensitivity. Data on antigen test utility is limited.

Other laboratory findings include leukopenia (leukocyte count is normal in majority), lymphopenia, elevated liver enzymes etc. Elevated C reactive protein (CRP), D-dimer, LDH, ferritin, troponin may indicate poor prognosis or risk of severe illness. Leukopenia may be masked in pregnancy as normal pregnant

women often have leucocytosis. D-dimer is elevated in normal pregnancy as well and hence interpretation of this has to be done with caution. When imaging is required, either Chest radiograph or CT scan of chest, it should be performed. The fetal radiation dose associated with these is negligible and it is not associated with fetal anomalies or loss.

MANAGEMENT:

Home care:

Asymptomatic or mildly symptomatic patients should have risk assessment done, closely monitored and can be managed at home with symptomatic treatment in the absence of obstetric problems. They should come for an obstetric follow up after two weeks of the infection. Those in third trimester should be advised to perform fetal kick count. They should be advised to access medical facility if fever persists >39 degree C, not able to tolerate oral feeds, have dyspnoea, persistent tachycardia>100, SPO2<95%, confusion or when an obstetric complication occurs.^{1,3}

Hospital care:

Women with co-morbidities or those with moderate, severe or critical illness should be hospitalised and managed in an ICU by a multidisciplinary team. The severe or critically ill pregnant woman should be managed similar to non-pregnant patients with respect to respiratory and general care. Spo2 has to be maintained to >95% which is in excess of oxygen needs of the mother. An Arterial blood gas must be performed when needed and PaO2 should be maintained above 70 mmHg in order to maintain the required oxygen gradient across the placenta. Proning which has been found very useful in managing COVID patients with respiratory distress is difficult in pregnancy because of the gravid uterus. But it can be considered with appropriate padding at least up till 28 weeks for the benefit it is likely to offer.¹

Anticoagulant use:

This is indicated for hospitalised pregnant women prophylactically, unless there is a contra indication. Unfractionated heparin is preferred, especially close to term because of its short half-life. 5000-7500 units subcutaneously 12th hourly is the

recommended dose. If delivery is not imminent Low molecular weight heparin like enoxaparin can be given at the dose of 1mg/kg bodyweight once daily.

Dexamethasone use:

For those requiring oxygen, steroids are indicated. If there is a need for the use of steroids for fetal lung maturity in addition, four doses of dexamethasone 6 mg can be administered at 12 hours interval and the dose can be completed thereafter for ten days once daily.³ There have been suggestions to use steroids like prednisolone 40 mg orally or hydrocortisone 80 mg twice daily (intravenously) for 10 days to reduce fetal exposure as these do not cross placenta when administration for fetal lung maturity is not indicated.

Remdesivir:

This is a novel nucleoside analog and if there is an indication for use of this drug, it can be used, though all trials using this for COVID excluded pregnant and lactating women. There is no reported fetal toxicity and this data comes from women who were given the drug during Ebola outbreak.³

Favipiravir:-This oral nucleoside analog initially used for Influenza, was tried without much benefit in COVID in the non pregnant patients, however the use of this is contraindicated in pregnancy.

Other drugs:

Tocilizumab: It is an interleukin-6 antagonist which is used in severely and critically ill patients with high inflammatory markers¹ but it crosses the placenta and can affect the fetal immune response. There is one study of use of this drug in pregnancy with COVID which did not suggest any safety concern but still it is indicated for cautious use.⁹ The Royal College of Obstetrician and Gynecologists strongly advocates its use in ICU patients with increased C Reactive Protein of more than 75 mg/l¹.

Baricitinib: It is a JAK inhibitor and it can be used in combination with remdesivir for hospitalised patients. Information on safety is limited and anecdotal and it has to be used with caution and after shared information.

Monoclonal antibody cocktail:-This is a cocktail of two antibodies, Casirivimab and Imdevimab,

designed specifically to block infectivity of SARS-CoV2. The data on use in pregnancy is limited and should be used only if there is potential benefit.¹ The other combination is Bamlanivimab- etesvimeb which was used for high risk patients who had a possibility to progress to severe disease as an out-patient treatment in mild to moderate disease .The use was suspended in United States because of likely resistance.

Convalescent plasma: There are some reports of use of this in pregnancy without confirmed benefits.

As mentioned earlier since most drug trials for COVID did not include pregnant women, the decision has to be based on individual case scenario depending on risk versus benefit.

Antenatal care:

Since antenatal care necessitates frequent hospital visits , during the pandemic there has to be a change made to provide quality and uncompromised care with minimal exposure of the woman to the risk of infection. Limiting frequency of visits to hospital depending on risk stratification in the initial visit, educating women on self-care, infection prevention methods and planning of subsequent visits for ultrasound, lab investigation, vaccinations together and offering tele-consults and physical consults as the situation demands have all been the changes witnessed in caring for antenatal women during the pandemic.

Drug safety for the Fetus:

The FDA Pregnancy drug risk categories to indicate potential risk to fetus which was used till 2015 has been replaced by the Pregnancy and Lactation Labelling Final Rule which is more descriptive (PLLR). But because of the familiarity with the earlier system, the few drugs which have an assigned risk used in pregnancy are mentioned here. (Table 1)

DELIVERY ISSUES:

Pregnant women with mild to moderate COVID-19 illness and in labour do not need alteration of mode of delivery. The mode of delivery can be vaginal. If induction procedures are required it is better to plan an elective caesarean section because of the higher chances of hospital staff getting exposed to

Table 1: Drugs and Fetal Risk.

DRUG	RISK CATEGORY
Corticosteroids	C/D
Heparin	B
Remdesivir	Not assigned
Favipiravir	Not assigned
Tocilizumab	C
Monoclonal antibodies	Not assigned
Baricitinib	Not assigned
Convalescent plasma	Not assigned
Supplements like vitamin C/Zinc	A
FDA categorisation.	

infection during induction. The timing of delivery in critically ill mothers or mothers on ventilatory support has to be decided by the treating team on an individual case basis. Delivery in these situations may be beneficial because this reduces the stress on cardiorespiratory system. In mild symptomatic patients, it is better to avoid postponing scheduled delivery for medical indications as illness may worsen during the second week. Neuraxial anaesthesia is preferred for analgesic and anaesthetic purpose as general anaesthesia is considered an aerosol generating procedure hence appropriate personal protective equipment needs to be used. In critically ill women with COVID-19 and preeclampsia, magnesium sulphate should be used with caution as it can cause respiratory depression.

POSTPARTUM AND BREAST FEEDING CONCERN:

Asymptomatic and mildly symptomatic women need to be monitored like any other woman postnatally, those with moderate illness should have continuous SpO₂ monitoring and further decision should be made according to the clinical status, and severe and critically ill patients should be managed according to protocol. Thromboprophylaxis with low molecular weight heparin needs to be administered in postpartum period in women with COVID-19. In patients with postpartum haemorrhage, some authors suggest avoiding tranexamic acid as it may increase risk of thrombosis in women with COVID-19.

There is no evidence to suggest transmission of infection through breast milk. Most breast milk specimens from infected mothers tested negative for SARS-CoV-2 RNA. Expressed breast milk feeding is preferred but if mother chooses to breast feed directly, she should use a mask, gown, follow hand hygiene and minimise duration of contact with the neonate. Post discharge, mother should adhere to the isolation protocol.

CARE OF PREGNANT HEALTH CARE WORKERS (HCW):

There are no guidelines regarding Pregnant HCW. Where personal protective equipment facilities are available, they can work in clinical areas. When other trained staff are there who can replace them, they should not be the first responders and also where high-risk procedures like aerosol generation are involved their exposure should be limited. It should be ensured that they are also vaccinated.

VACCINATION:

There is enough data now regarding the safety and requirement for vaccination in pregnant women. Out of the three vaccines available currently in India, Covaxin is an inactivated vaccine and Covishield and Sputnik V are non-replicating viral vector platform vaccines.¹⁰ Pregnant women should be guided to make an informed decision by discussing the consequences of infection, the advantages of vaccination and also the possible side effects. A woman who is willing for vaccination can take it anytime in pregnancy. There should be systematic

reporting of adverse events occurring after immunization (AEFI). The National AEFI surveillance operational guidelines and COVID-19 vaccination operational guidelines will be followed for AEFI surveillance related to COVID-19 vaccination of pregnant women.

When the vaccination programme was initiated in January 2021 in India pregnant women were not included. Subsequently, data which emerged from different studies showed that vaccination in antenatal women had more benefits than risks and also the disease followed a more severe course among pregnant women than the non-pregnant women of the same age group. Based on the recommendations of the National Technical Advisory Group on Immunization (NTAGI), Union Health Ministry approved vaccination in pregnant women from July 2021. It is suggested that if the woman has been affected with infection during the current pregnancy, she can receive the vaccine after delivery. The data available now does not suggest any risk to the mother or fetus.³ Though there are mild side effects associated with vaccine administration, the long term consequences are not currently known. The side effects requiring immediate medical attention which may occur rarely or the contraindications for vaccination are like that of general population. Globally there is consensus among all professional bodies in favour of vaccinating pregnant women. There is no need to do pregnancy testing before vaccination in women of reproductive age group. The practice of infection prevention methods should be adhered to after vaccination also. There is also no data which suggest any association between vaccination and infertility. The vaccines used in other countries have also been found to be safe in pregnancy.

CONCLUSION:

Pregnancy poses additional challenges in view of prolonged care, need for frequent visits to the health care facility and involves health of mother and fetus. Though the overall risk of severe illness is not high, women in the antenatal and post-partum period have a risk of severe illness compared to non-pregnant women. There are certain factors which increase this risk. Preterm births have been found to be common. Though information on commonly

used drugs for COVID in pregnancy is limited, when indicated for maternal benefit they should be used. Infection prevention practices and management is similar to that of non-pregnant patients. Women should be encouraged to go for vaccination and wherever possible technology should be embraced for care of these women.

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COVID-19 IN PREGNANCY

- 1. True about COVID-19 in pregnancy –**
 - a. Tends to be mild illness in most
 - b. 50% of pregnant women develop severe illness if infected
 - c. Pregnant women are at less risk of acquiring infection
 - d. Infection in first trimester is an indication for termination
- 2. Best test to diagnose COVID-19 in pregnancy is**
 - a. SARS-CoV-2 RTPCR nasopharyngeal swab
 - b. Rapid antigen test
 - c. IgM antibody test
 - d. IgG antibody test
- 3. Marker which is a predictor of severe illness – except**
 - a. Leukocytosis
 - b. Elevated ferritin
 - c. Elevated D-Dimer
 - d. Elevated CRP
- 4. True about COVID-19 in pregnancy –**
 - a. Mainstay of treatment is symptomatic and supportive
 - b. Increased mortality in pregnancy
 - c. Steroids should be avoided even in critically ill women
 - d. All are true
- 5. Management of severely ill pregnant women includes**
 - a. Remdesivir can be offered on compassionate basis
 - b. Prednisolone may be preferred to dexamethasone as dexamethasone crosses placenta
 - c. Prophylactic anticoagulation

- d. All the above
- 6. Mode of delivery in pregnant women with COVID-19 should be-**
 - a. LSCS
 - b. Vaginal delivery
 - c. Depends on obstetric indication
 - d. Assisted vaginal delivery
- 7. Regarding transmission of SARS-CoV-2 from mother to baby – false statement is**
 - a. vertical transmission is well known
 - b. transmission through breast milk is well documented
 - c. virus has not been detected in breast milk
 - d. all the above
- 8. true about breast feeding in COVID-19 mothers**
 - a. breast feeding is contraindicated
 - b. expressed breast milk feeding should be considered
 - c. direct breast feeding should not be allowed even if mother prefers it (with all due precautions)
 - d. all the above
- 9. True statement about timing of delivery in COVID-19 mothers**
 - a. Scheduled inductions and caesarian sections for medical indication should not be postponed in asymptomatic mothers
 - b. Scheduled Deliveries should be postponed in mild symptomatic mothers
 - c. In critically ill mothers on ventilator at term pregnancy, LSCS is contraindicated
 - d. All of the above
- 10. True about antenatal care in covid period**
 - a. Routine antenatal visits should be avoided
 - b. Teleconsultation facilities should be utilized where ever feasible
 - c. Quarantine guidelines are different for pregnant mothers
 - d. All the above

KEY: 1. a; 2. a; 3. a; 4. a; 5. d; 6. c; 7. d; 8. b;
9. a; 10. b;

Management of COVID-19 positive children



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Few cases of COVID-19 caused by SARS-CoV-2 infection have been reported in children compared with the total number of cases in the general population. The majority of SARS cases in children younger than 18 were thought to have occurred through household transmission, though some cases were hospital-acquired. Data from paediatric cases of COVID19 show milder symptoms among children compared with adults. Co-detection of other respiratory pathogens (influenza, respiratory syncytial virus, Mycoplasma pneumoniae) has been described in children with COVID-19. Among various studies across world, deaths occurred among children with critical illness and the overall case fatality rate was 2.3%. The case fatality rate among children with critical disease was 49%. Among children in China, illness severity was lower with 94% having asymptomatic, mild or moderate disease, 5% having severe disease, and <1% having critical disease. Very few cases of death have been reported in children in present pandemic of COVID 19.

Clinical course

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset. The signs and symptoms of COVID-19 present at illness onset vary, but over the course of the disease.

The presentation of covid-19 in children is very much varied from asymptomatic children to Covid pneumonia. Usually they present with fever, headache, myalgia, fatigue, tiredness, coryza, cough, sore throat & sometimes with breathlessness.

Intestinal symptoms are being reported in most of the children in 2nd wave like diarrhoea, vomiting, abnormal pain. Loss of taste or smell has also been reported in some children. Few children are having rash, conjunctival congestion, mucositis and some

of these presented only with pain in knee/backache. High index of suspicion is required to diagnose covid-19 in children.

Common presentation of covid in children

- Usually features of flu like symptoms fever, headache, bodyache, myalgia, extreme weakness, sore throat & breathlessness.
- GI symptoms are predominant in some children eg. Vomiting, diarrhoea, pain in children.
- Eye symptoms like conjunctival congestion.
- Pain in knee joint/backache rarely.
- Loss of taste or smell in older children.

In neonates

- Usually asymptomatic.
- 15% with fever, poor feeding, lethargy & gastrointestinal symptoms.

Illness Severity

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnoea, hypoxia, or >50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multi organ system dysfunction): 5%

Children with no reported underlying medical conditions had lower case fatality rate, but case fatality was higher for children with comorbidities like cardiovascular disease, chronic respiratory disease, chronic kidney disease, immunocompromised states, etc. Among children who developed severe disease, the medium time to develop dyspnoea ranged from 5 to 8 days, the median time to acute respiratory distress syndrome (ARDS) ranged from 8 to 12 days, and the median

time to ICU admission ranged from 10 to 12 days. Clinicians should be aware of the potential for some children to rapidly deteriorate within one week after the onset of illness. The median length of hospitalization among survivors was 10 to 13 days.

Children may play a role in the spread of SARS-CoV-2 in the community as viral RNA was detected in respiratory specimens up to 22 days after symptoms began and in stool up to 30 days after symptoms began according to some studies. Although transmission of SARSCoV-2 from asymptomatic or pre-symptomatic persons has been reported, risk of transmission is thought to be greatest when children are symptomatic. Viral RNA shedding, measured indirectly by RT-PCR cycle threshold values, is greatest at the time of symptom onset and declines over the course of several days to weeks.

Clinical recovery has been correlated with the detection of IgM and IgG antibodies which signal the development of immunity. However, overall control of pandemic depends of development of herd immunity either by infection or mass immunization (under research process). There are no data concerning the possibility of re infection with SARS-CoV-2 after recovery from COVID-19.

Moderate disease

- Mild pneumonia
- Symptoms such as fever, cough, fatigue, headache and myalgia
- No complications and manifestations related to severe infections

Severe disease

- Mild or moderate clinical features plus any manifestations that suggests disease progression
- Rapid breathe (>70 breaths per minute for infants aged less than 1 year,> 50 breaths per minute in children more than 1 year)
- Hypoxia
- Loss of consciousness, Depression, coma, convulsions
- Dehydration, difficulty feeding, gastrointestinal dysfunction

- Myocardial injury
- Elevated liver enzymes
- Coagulation dysfunction, rhabdomyolysis and any other manifestations suggesting injuries to vital organs

Critical illness

Rapid disease progression plus any other conditions

- Respiratory failure with need for mechanical ventilation (e.g. ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or through mask)
- Septic shock
- Organ failure that needs monitoring in ICU

Basic workup

Detailed history of onset of symptoms and progression in a chronology has to be obtained. History and medical documents should be obtained in order to classify the COVID19 positive children in to high risk and no risk group.

Diagnostic Testing Diagnosis of COVID-19 requires detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR). Detection of SARS-CoV-2 viral RNA is better in nasopharynx samples compared to throat samples. Lower respiratory samples may have better yield than upper respiratory samples. SARS-CoV-2 RNA has also been detected in stool and blood. Detection of SARS-CoV-2 RNA in blood may be a marker of severe illness. Infection with both SARS-CoV-2 and other respiratory viruses has been reported, and detection of another respiratory pathogen does not rule out COVID-19

Laboratory investigations

- **Base line investigations:** CBP, CRP, ESR, S. Ferritin, Procalcitonin, SGPT, SGOT, Creatinine phosphokinase, LDH, Blood culture D-dimer, Random blood glucose
- **In severe cases:** Coagulation function, Baseline ECG, Myocardial enzyme spectrum, Blood gas analysis, Serum electrolytes.

Lymphopenia is the most common lab finding in COVID-19 and is found in as many as 83% of hospitalized children. Lymphopenia, neutrophilia,

elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high CRP, and high ferritin levels may be associated with greater illness severity. Elevated D-dimer and lymphopenia have been associated with greater morbidity and mortality. Procalcitonin is typically normal on admission, but may increase among those admitted to the ICU. Children with critical illness has high plasma levels of inflammatory makers, suggesting potential immune dysregulation.

Radiographic findings

Chest X-rays of children with COVID-19 show patchy infiltrates consistent with viral pneumonia. Chest radiographs typically demonstrate bilateral air-space consolidation, though children may have unremarkable chest radiographs early in the disease. Chest CT images from children with COVID-19 typically demonstrate bilateral, peripheral nodular ground glass opacities. Because this chest CT imaging pattern is nonspecific and overlaps with other infections, the diagnostic value of chest CT imaging for COVID-19 may be low and dependent upon interpretations from individual radiologists. Given the variability in chest imaging findings, chest radiograph or CT alone is not recommended for the diagnosis of COVID-19.

Management

COVID-19 positive children may be asymptomatic or may develop mild illness. Mild illness include uncomplicated upper respiratory tract viral infection symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnoea, nasal congestion, or headache. Rarely, children may also present with diarrhoea, nausea, and vomiting.

WHO recommends that all laboratory confirmed cases be isolated and cared for in a health care facility. The decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability of the parents to isolate the children at home. Children with risk factors for severe illness should be monitored closely given the possible risk of progression to severe illness in the second week

after symptom onset.

Children with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and will be able to manage the illness at home. Asymptomatic or mild symptomatic COVID children can be isolated and managed either in hospital or in non-traditional facilities, such as repurposed hotels, stadiums or gymnasiums with adequate basic health facilities and medical staff, where they can remain until their symptoms resolve and laboratory tests for COVID-19 virus are negative.

Triaging for home based care or basic level health facility based on investigations:

- Lymphocyte count > 1100/uL2, Neutrophilia/ Lymphocyte ratio <3, no thrombocytopenia,
- Normal d-dimer,
- CRP < 60mg/L,
- Normal CXR

Treatment:

- Bed rest
- Supportive care
- Adequate calorie (Nutrition) and water intake
- Antipyretics – Paracetamol – 10-15mg/kg/ dose

Home based care

Home based care can be considered, as long as they can be followed up and cared for by family members. This decision requires careful clinical judgment and should be informed by an assessment of the safety of the patient's home environment. In cases in which care is to be provided at home, if and where feasible, a trained HCW should conduct an assessment to verify whether the residential setting is suitable for providing care; the HCW must assess whether the patient and the family are capable of adhering to the precautions that will be recommended as part of home care isolation (e.g., hand hygiene, respiratory hygiene, environmental cleaning, limitations on movement around or from the house).

- Where testing is not possible, WHO recommends that confirmed children remain

isolated for an additional two weeks after symptoms resolve.

Hospital based care

Indications for hospital admission

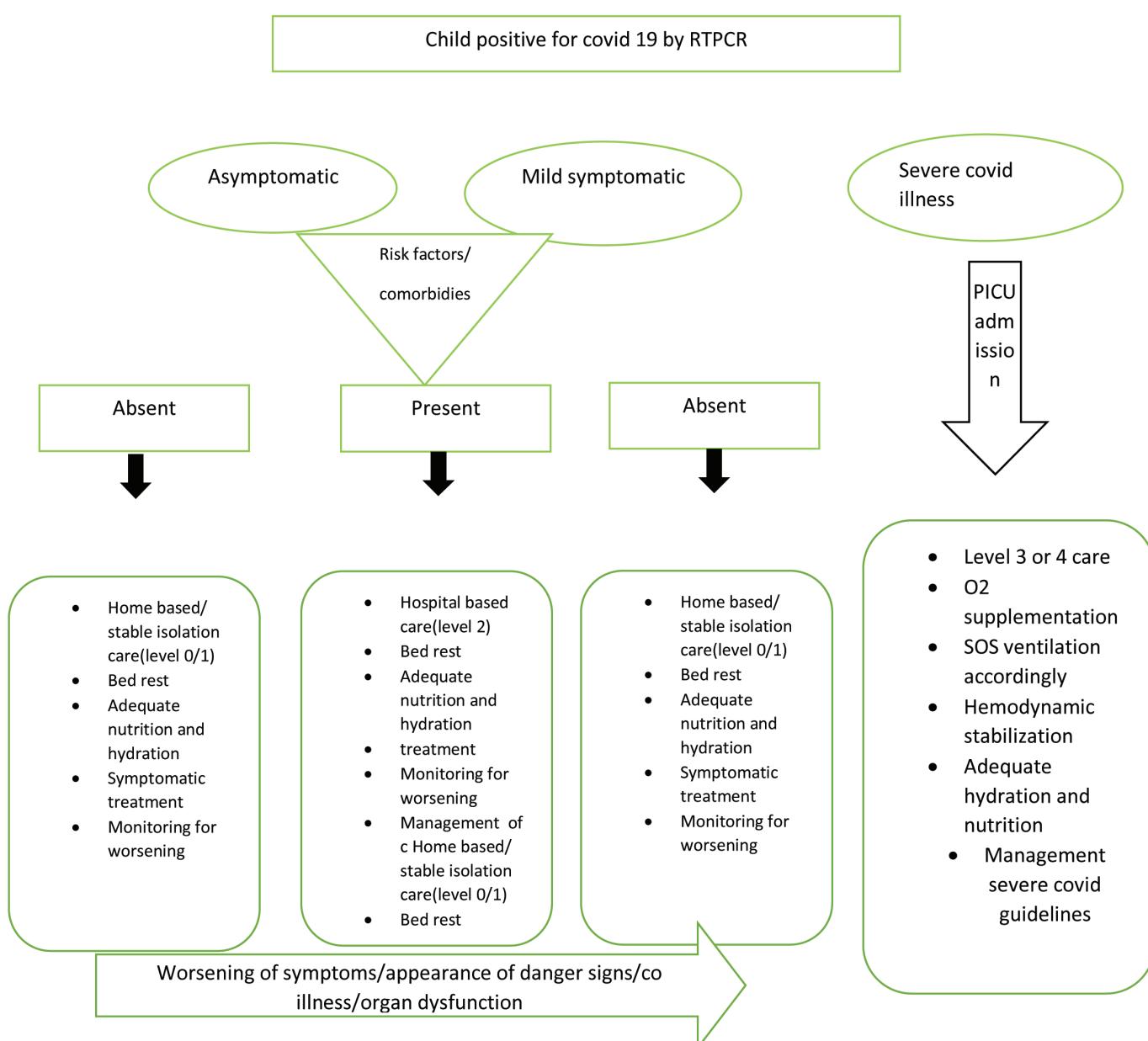
- Respiratory distress
- SpO₂ < 94% on room air
- Shock/ poor peripheral perfusion
- Poor oral intake, especially in infants and young children
- Lethargic, especially in infants and young children
- Seizures/ encephalopathy
- Children with high risk for severe disease with mild symptoms:
 - congenital or acquired heart disease,
 - chronic lung, liver, kidney or neurological disease,
 - immunosuppressive drugs,
 - congenital or acquired immunodeficiency

Indications for PICU Admission

- Moderate to severe ARDS requiring mechanical ventilation
- Shock requiring vasopressor support
- Worsening mental status
- Multi-organ dysfunction syndrome
- MIS-C
- Worsening mental status
- Multi-organ dysfunction syndrome
- MIS-C
- At triage give suspect patient a triple layer surgical mask and direct patient to separate area, an isolation room if available.
- Keep at least 1meter distance between children. Instruct all children to cover nose and mouth during coughing or sneezing with tissue or flexed elbow for others. Perform hand hygiene after contact with respiratory secretions.

- Droplet precautions prevent large droplet transmission of respiratory viruses. Use a triple layer surgical mask if working within 1-2 meters of the patient.
- Place children in single rooms, or group together those with the same etiological diagnosis.
- When providing care in close contact with a patient with respiratory symptoms (e.g. Coughing or sneezing), use eye protection (facemask or goggles), because sprays of secretions may occur. Limit patient movement within the institution and ensure that children wear triple layer surgical masks when outside their rooms
- Droplet and contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e. contact with contaminated oxygen tubing/ interfaces). Use PPE (triple layer surgical mask, eye protection, gloves and gown) when entering room and remove PPE when leaving. If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers).
- If equipment needs to be shared among children, clean and disinfect between each patient use. Ensure that health care workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloved or ungloved hands.
- Avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches). Ensure adequate room ventilation. Avoid movement of children or transport. Perform hand hygiene.
- Ensure that healthcare workers performing aerosol-generating procedures (i.e. open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators.
- Whenever possible, use adequately ventilated

- single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation. Avoid the presence of unnecessary individuals in the room.
- Symptomatic treatment, bed rest, adequate hydration and nutrition remain the cornerstone.
 - A health care worker should regularly assess the child for worsening symptoms or presence of co-infection/illnesses.
 - Children should be escalated to higher level health care unit in settings of clinical worsening. Management approach for a child confirmed with covid 19



Discharge criteria

- After 10 days of symptom onset, AND
- Clinical resolution of symptoms, AND
- SpO₂> 95%, off oxygen for 3 days
- Followed by home isolation and self-monitoring for 7 days appropriate IPC measures.

MIS-C; WHO criteria

- Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
- Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
 - i Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

- Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

- No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

- Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Care of infants with covid-19 positive mother

- Considering the benefits of breastfeeding and the insignificant role of breast milk in the transmission of other respiratory viruses, a mother can continue breastfeeding.
- Infants born to mothers with suspected, probable, or confirmed COVID-19 should be fed according to standard infant feeding

guidelines, while applying necessary precautions for IPC.

- Mother should wear a medical mask when she is near her baby and perform hand hygiene before and after having close contact with the baby. She will also need to follow the other hygiene measures described in this document.
- Mothers and infants should be enabled to remain together and practice skin-to-skin contact, kangaroo mother care and to remain together and to practice rooming-in throughout the day and night, especially immediately after birth during establishment of breastfeeding, whether they or their infants have suspected, probable, or confirmed COVID-19.
- Breastfeeding counselling, basic psychosocial support, and practical feeding support should be provided to all pregnant women and mothers with infants and young children, whether they or their infants and young children have suspected or confirmed COVID19.
- In situations when severe illness in a mother with COVID-19 or other complications prevents her from caring for her infant or prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and safely provide breast milk to the infant, while applying appropriate IPC measures

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COVID-19 in the Long Run from Foresight to Hindsight



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From the moment it was declared a pandemic of global proportions on a fateful March day in 2020, COVID-19 has baffled leaders in every field of expertise involving the human condition. Even as scientists and healthcare workers continue to grapple with the scale and destructive magnitude of its ominously recurring 'waves', SARS-CoV-2 continues to expose novel challenges - yet to be understood - in the slow burning aftermath of its devastation.

From trying to offset the immediate threat of its mortality rate during the height of the COVID-19 pandemic to mitigating the impact of longterm debility among its survivors, we've experienced a drastic shift in perspective - one that has redirected our focus from diligent foresight to reflective hindsight.

The Ongoing COVID Conundrum

While several other viral infectious diseases have been shown to cause persisting symptoms following an acute phase, the sheer case burden of COVID-19 survivors and the longterm sequelae plaguing them has merited the distinction of **Long COVID** as an emerging health crisis. What started out as a patient-coined phenomenon in May 2020 has evolved into a formally recognised clinical entity with the CDC calling it an umbrella term for 'a wide range of health consequences that are present four or more weeks after infection with SARS-CoV-2 which include-

- Long Covid (which consists of a wide range of symptoms that can last weeks to months) or persistent post-Covid syndrome (PPCS) or Chronic COVID Syndrome
- Multi-organ effects of COVID-19
- Effects of COVID-19 treatment/hospitalisation

It covers a diverse group of COVID cases, with

overlapping symptom profiles, whose clinical presentation of acute illness has ranged from mild, asymptomatic disease to a severely critical course requiring hospitalisation. What's interesting to note, in fact, is how some studies show minimal differences between the prevalence of long covid symptoms between hospitalised and non-hospitalised covid-19 patients.

NICE divides Long COVID into 2 subgroups based on the duration of signs and symptoms that continue or develop after acute COVID-19 — a.) Subacute Symptomatic COVID-19 that lasts between 4-12 weeks following initial infection and b.) Post-COVID-19 Syndrome that is used to refer to clinical features that persist for longer than 12 or more weeks after onset.

A Kaleidoscope of Symptoms

As the percentage of recovered cases outnumber that of fresh infections, a renewed spotlight on the post-acute phase of COVID-19 has opened up a flow of data that is now enabling us to gauge the lasting implications of this disease beyond the scope of hospital care. While its definition and our perception of the bigger picture continues to evolve, several studies have shown that Long COVID is marked by a wide spectrum of lingering features spanning the breadth of clinical severity and ranging across organ systems.

A study published by The Lancet earlier this year has identified more than 200 symptoms as part of what it calls 'Post-acute COVID-19 sequelae' and attempts to characterise these complaints into clusters based on prevalence and time course. The most widely observed symptoms include fatigue, post-exertional malaise, loss of taste or smell, shortness of breath, chest pain, brain fog, memory issues, insomnia, head aches, joint pains and muscular weakness - features that have been shown

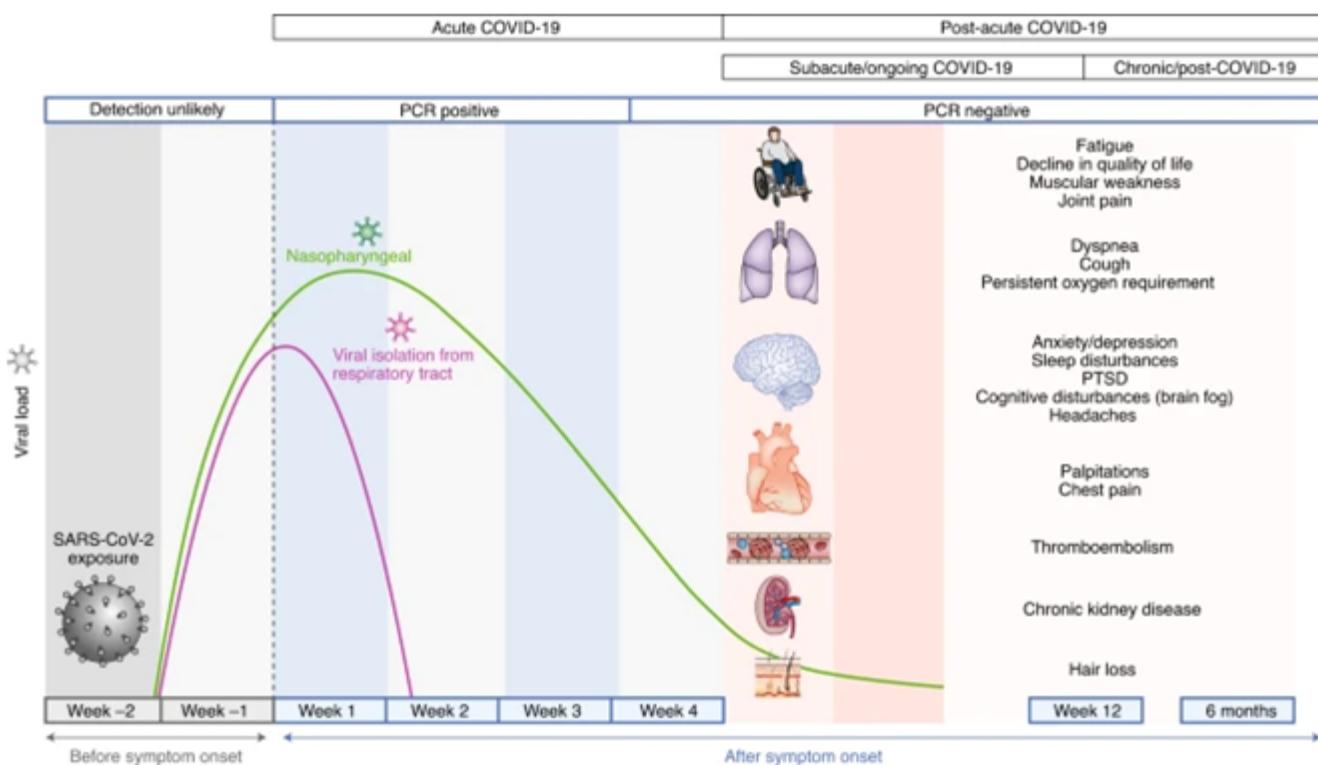


Figure 1 - Timeline of acute and post-acute COVID-19 (Source - Nature Medicine 27, pages 601–615 (2021))

to persist anywhere between 4 weeks to 12 months or longer post-infection and could not be explained by an alternative diagnosis.

Several risk factors have been identified that predispose an individual to develop Long COVID. Due to a paucity of existing evidence, these factors

include but are not limited to age (>70 years), female sex, obesity, pre-existing respiratory illnesses such as asthma. With the rise of newer mutant strains have arisen questions about their ability to cause more damaging longterm complications than their predecessors.

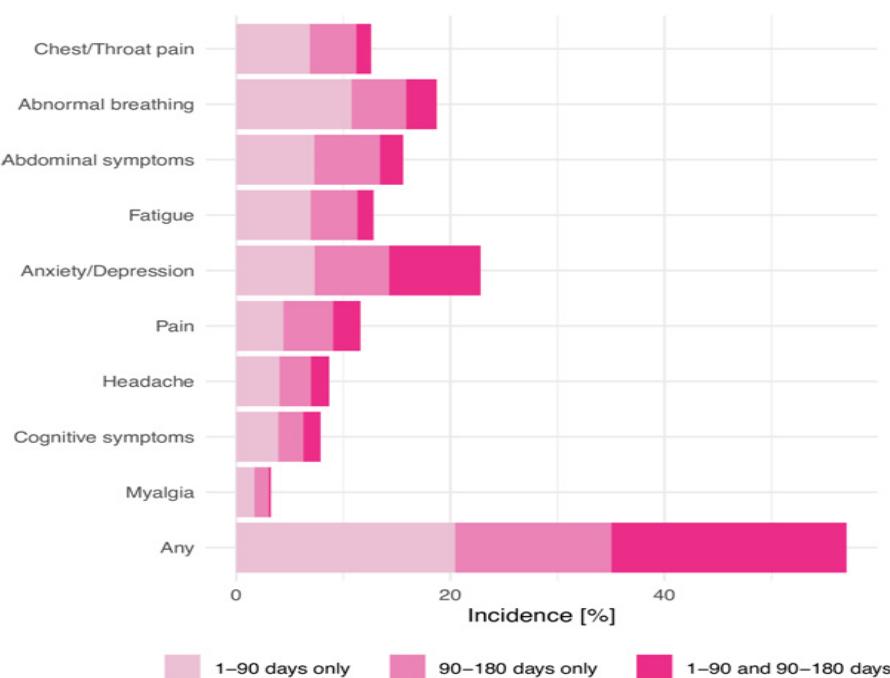


Figure 2 - Incidence of each long-COVID feature in the 180 days following COVID-19 (Source - PLOS Medicine, September 2021)

A review article published in Nature Medicine categorises these sequelae into several groups depending on the organ system involved-

Pulmonary Involvement

- Shortness of breath, diminished exercise capacity and hypoxia are commonly persistent features.
- A reduction in diffusion capacity, restrictive pathological changes in the lungs, ground-glass opacities and fibrotic changes on HRCT have been observed during follow up visits.

Haematological Involvement

- Thromboembolic events have also been observed in post-acute COVID cases.

Cardiovascular Involvement

- Shortness of breath, fatigue, myocarditis, reduced cardiac reserve, autonomic dysfunction, and arrhythmias have been shown to result from cardiovascular damage.
- Long-term sequelae also include increased cardiac metabolic demand, myocardial fibrosis or scarring (detected via cardiac MRI) and dysregulation of the renin-angiotensin-aldosterone system(RAAS).
- A collection of case reports published in the Chest Journal details an alarming trend of acute myocarditis presenting with an acute non-ischemic left ventricular dysfunction and a troponin elevation at admission among patients who had recent history of confirmed SARS-CoV-2 infection. In feasible cases, the diagnosis of myocarditis was confirmed through cardiac MRI by the presence of diffuse oedematous changes in the myocardium - a pattern of inflammation that ruled out ischemic injury, stress-induced cardiomyopathy, or type 2 myocardial infarction.
- Furthermore, it has been observed that heart disease develops and progresses quickly post-COVID disease and this has been attributed to the inflammatory and pro-coagulant state characteristic of COVID-19.

Neurocognitive Involvement

- Persistent complaints include fatigue, myalgia, headache, autonomic dysfunction and 'brain fog'.

- Inflammatory damage, triggered by acute infection, would cause psychiatric disorders in predisposed individuals. These symptoms include attention deficits, depression, anxiety, post-traumatic stress disorder and, in worse situations, suicidal behaviour.

Renal Involvement

- Resolution of Acute Kidney Injury during acute COVID-19 occurs in a majority of patients; however, reduced eGFR has been observed during follow up visits.

Endocrine Involvement

- Endocrine involvement may disrupt glycemic control in diabetics, worsen cases of thyroiditis and bone demineralisation
- Post-viral destruction of β cells of pancreas may also trigger the development of diabetes mellitus.

Gastrointestinal and Hepato-biliary Involvement

- Prolonged viral faecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing
- COVID-19 has been shown to disrupt the intestinal microbiome, promoting the growth of opportunistic organisms and hindering that of healthy commensals. Several studies have been proposed to establish a correlation between COVID-19 and post-infectious irritable bowel syndrome and dyspepsia.

Effects on Skin and Hair

- COVID-19 has also been identified as a stressor that leads to telogen effluvium, with skin rash being another common dermatological complaint.

Multi-system Inflammatory Syndrome in Adults

Multi-system inflammatory syndrome (MIS) is severe but rare complication of SARS-CoV-2 that is known to occur 2–12 weeks after initial infection. A series of case reports published by the CDC late last year documented this phenomenon of hyper-inflammation and extra-pulmonary organ dysfunction in patients who - unlike hospitalised cases of severe COVID-19 - had minimal respiratory symptoms, hypoxemia or radiographic abnormalities. The underlying mechanism for this syndrome has been attributed to endothelial

damage, thrombo-inflammation, dysregulated immune responses, and dysregulation of the renin-angiotensin-aldosterone system. The CDC has developed a working case definition for MIS A which broadly includes:

- Age 21 years or older;
- Presence of a severe illness requiring hospitalisation;
- Recent confirmed SARS-CoV-2 infection (RT-PCR, RAT or Antibody Test);
- Severe extra-pulmonary organ dysfunction;
- Markedly elevated acute inflammatory markers; and/or
- Absence of severe respiratory illness (to differentiate it from organ dysfunction caused by tissue hypoxia)

Demystifying the Post-COVID Fog

A multitude of studies have been undertaken to deepen our knowledge of COVID-19 and its underlying pathophysiology. Several parallels exist between the post-acute illness brought on by SARS-CoV-2 and the longterm sequelae associated with other viral infections - the most pertinent of which is the original SARS Coronavirus that was the culprit behind the 2003 SARS Outbreak. In the wake of its damaging course, SARS left behind a slew of survivors languishing in a post-viral nightmare that crippled their ability to return to normalcy. This wave of persisting complaints triggered an interest in what was termed 'Post-SARS Sickness'.

Taking cue eighteen years later, current research on Post-COVID Sequelae is aimed at defining and elucidating the mechanism behind post-viral

illnesses such as those triggered by SARS-Coronaviruses, Epstein Barr Virus, Ebola virus et al. and their possible role in the development of lesser understood medical conditions such as Chronic Fatigue Syndrome.

The pathogenesis of post-COVID syndrome is multifactorial and an interconnected web of mechanisms has been implicated in the development of several clinical manifestations. So far, conclusions drawn from observed patterns have implicated cellular damage, a prolonged pro-inflammatory cytokine response, endothelial dysfunction, a pro-coagulant state, an autoimmune phenomenon or even a hormonal imbalance as a consequence of an alteration in the hypothalamic-pituitary-adrenal axis induced by SARS-CoV-2 infection as contributing factors of Long COVID.

It is plausible that most of the inflammatory response caused by the virus affects the integrity of the central and peripheral nervous system, which promotes the perpetuation of pain after the acute illness. Alteration of neuronal function due to an increase in circulating cytokines, IL-6 in particular which can cross the blood-brain barrier, may lead to neuromotor and cognitive fatigue, and explain apathy and executive dysfunction. The hippocampus appears to be particularly vulnerable to infection, which may lead to memory deficit.

Sustained elevation of IL-6 levels, an increase in ACE-2 levels in the peripheral nervous system and mast cell participation have been identified to explain the musculoskeletal symptoms in Post COVID Syndrome.

Longterm fatigue may also be attributed to lung

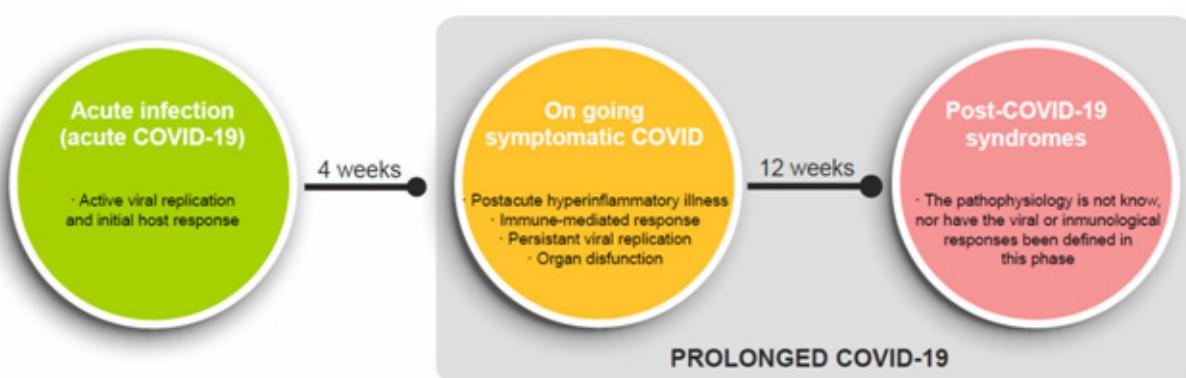


Figure 3 - Pathogenesis of Post-COVID Syndrome (Source - International Journal of Environmental Research and Public Health 2021, 18(10), 5329)

dysfunction which results from endothelial injury, diffuse alveolar damage and fibrosis following recovery. A reduction in diffusion capacity is the most common physiologic dysfunction in post-acute COVID-19 and has been correlated with the severity of acute disease.

Overlap with Post-Intensive Care Syndrome

Patients recovering from critical illness requiring prolonged intensive care, particularly those with cerebral dysfunction, tend to experience a combination of psychological, cognitive and physical signs and symptoms that may persist for months to years following the period of acute illness, a condition known as 'Post-Intensive Care Syndrome'. As a result of similarity in profile, this phenomenon is also being studied as a possible factor in the development of post-COVID syndrome among patients recovering from severe COVID-19 illness.

Managing Their Misery

As our understanding of Post-COVID syndrome continues to evolve, it remains a diagnosis of exclusion, one that can be reached only after all other possible causes have been ruled out. In the same vein, no concrete guidelines currently exist regarding its management.

While this can prove to be a frustrating process, both for the treating physician and the one being treated, due diligence is a service owed to every individual seeking medical care. A detailed clinical history regarding the onset and duration of current symptoms, underlying co-morbidities, the severity of COVID-19 must be elicited by healthcare providers during follow-up visits.

Multiple case reports have related reactivation and relapse of SARS-CoV-2 in COVID-19 recovered patients. Hence, reinfection with SARS-CoV-2 needs to be ruled out in addition to other secondary bacterial and fungal infections that have been commonly reported among such cases resulting from the immunocompromised state brought on by COVID-19.

Investigative modalities must include routine laboratory assessment with complete blood count (CBC), testing for liver, renal function, and a coagulation profile. Other tests such as CRP,

fibrinogen, D-dimer, troponin, and ferritin may also be considered if clinically indicated among patients whose symptoms persist beyond a few weeks.

Repeat pulmonary imaging, preferably with a high-resolution CT scan or CT Angiogram, can be considered in patients presenting with predominantly respiratory symptoms. Tests to assess cardiac function such as ECG and 2D Echo must also be utilised to rule out an underlying cardiopulmonary disease process. Neuroimaging modalities such as CT/MRI must be performed, whenever clinically relevant, in patients presenting with neurological manifestations.

In response to a growing clamour of voices signalling the existence of a post-acute illness, several countries have ventured to set up clinics dedicated to patients with complaints persisting even after recovery from COVID-19. In the UK, a multidisciplinary approach led to the establishment of a chain of 'Long COVID' clinics aimed at offering both physical and psychological assessments to long haulers and to refer them to appropriate treatment and rehabilitation services.

Since Long COVID results from a multi system dysfunction and has a variable presentation within the population, an effective treatment strategy must include individualised therapy that incorporates inter-professional care in a bid to address the patient's concerns holistically. In addition to this, the importance of healthy lifestyle changes such as a balanced diet, sleep hygiene, abstinence from smoking and alcohol must be reinforced during each visit.

Caring for Carers

Even as we continue to assess the damage that this pandemic has left in the ebb of its surging waves, we'd be remiss not to mention its impact on the mental and moral environment of healthcare workers who have had to make crucial decisions under unprecedented distress. The role of a physician has never been more all-encompassing - from providing healthcare and offering reassurance to patients and their families to pulling strings to arrange short stocked drugs and spreading public awareness and dispelling myths about COVID vaccines - healthcare workers have discharged the full spectrum of their professional and moral duties. With the dust now

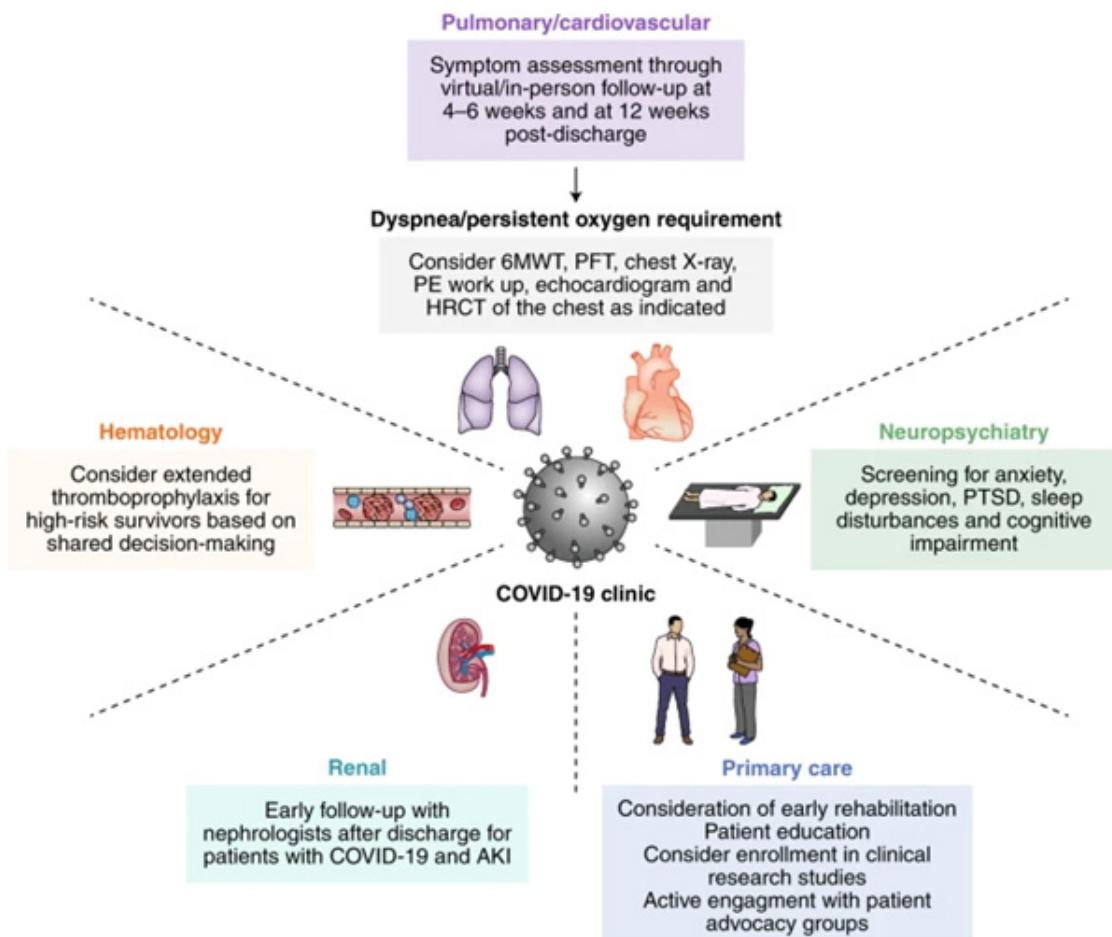


Figure 4 - Management Strategies for Post-Covid Syndrome (Source - Nature Medicine 27, pages 601–615 (2021)

beginning to settle, increasing rates of sleep disorders, attention deficit, memory issues, post traumatic stress, anxiety and depression have emerged among healthcare workers in the past year. A concerning issue has been that of physician burnout resulting from what the British Medical Journal calls 'moral injury' - arising from repeated exposure to ethical dilemmas created by the COVID crisis. Such trends underscore the need for regular evaluation of healthcare workers and the consequent establishment of measures to help them recover from their trauma.

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Covid-19 and Pulmonary Fibrosis

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INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. Coronavirus disease 2019 (COVID-19) was announced in March 2020 as a pandemic by the World Health Organization (WHO). Months later, longer-lasting COVID-19 cases started gaining attraction among social support groups, like Long Haul Covid Fighters, Body Politic Covid-19 Support Group. At first, doctors dismissed their concerns as symptoms related to mental health, such as anxiety, in a phenomenon called "medical gaslighting". But the scenario changed soon. The term long-haul COVID-19 (or post-acute COVID-19 or chronic COVID syndrome or long-COVID) started gaining recognition in the scientific and medical communities.

Maria Skaalum Petersen et al. (Clinical Infectious Diseases. 2020) reported in a study of 180 survivors that 53.1% developed symptoms of long-haul COVID-19 for at least 125 days since symptom onset, which was not associated with gender, smoking, co-morbidities, or medication use.

The recovery process from COVID-19 exists on a continuum-

- Acute COVID-19: symptoms of COVID-19 for up to 4 weeks following the onset of illness.
- Ongoing symptomatic COVID-19: symptoms of COVID-19 from 4 to 12 weeks following the onset of illness.
- Post-COVID-19: symptoms that develop during or after COVID-19, continue for ? 12 weeks, not explained by an alternative diagnosis.

PATHOGENESIS

The mechanism of post-viral lung fibrosis has been extensively studied in other related viral epidemics like influenza and SARS, and a knowledge of the past might educate us as we head into an unknown future. Looking first at severe H1N1, a study from China of 16 patients hospitalised with pneumonia caused by the 2009 H1N1 influenza showed high levels of transforming growth factor?beta 1 (TGF??1). This cytokine is known to induce fibrosis by various mechanisms which include increased deposition of extracellular matrix proteins, stimulation of fibroblast chemotactic migration, and fibroblast to myofibroblast transition.

Animal studies by Jolly et al. using a mouse model showed that the influenza virus stimulates toll?like receptor 3, which activates TGF??1 in the lungs, resulting in augmented levels of collagen deposition. In their experiments, they were able to demonstrate large increases in collagen I, III, IV, and VI, as early as 5 days post-influenza infection. In the earlier SARS-CoV?1 outbreak in 2002, high levels of TGF??1 were also observed in serum, bronchial epithelial cells, and alveolar epithelial cells.

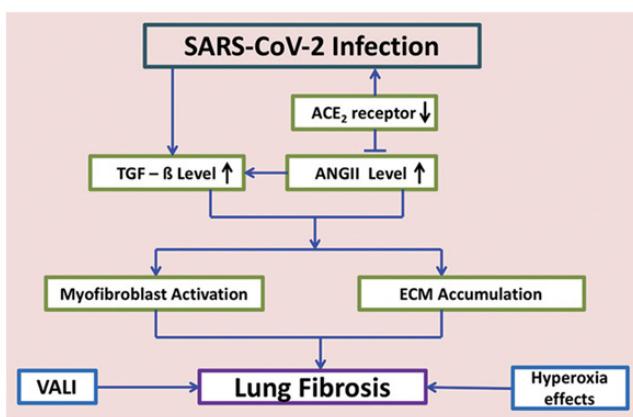


Figure 1: Pathogenesis of Lung Fibrosis

Two iatrogenic factors potentially contributing to the fibrosis encountered in survivors of severe COVID-19 pneumonia are oxygen toxicity and ventilator-induced lung injury (VILI). Patients who develop post-COVID fibrosis are invariably those who are sicker, have extensive, bilateral involvement initially, and hence are more likely to have required high concentrations of oxygen, often for prolonged periods of time during the acute stage of their illness.

Extended exposure to high concentrations of oxygen is known to result in heightened production of oxygen-derived free radicals which can damage the pulmonary epithelium. The sickest patients with acute respiratory distress syndrome (ARDS) from COVID-19 pneumonia are also more likely to have required prolonged mechanical ventilation, often with generation of high plateau pressures in attempts to ventilate their stiff, noncompliant lungs.

The role of mechanical stress as an inciting factor for lung injury is also well recognised and it is likely that VILI may also be contributing to the pulmonary fibrosis encountered in these patients. (Table 1)

RISK FACTORS

In a study by Zou J-N, Sun L, Wang B-R, Zou Y, Xu S, Ding Y-J, et al, the following factors were found in patients with post covid fibrosis. Multivariate binary logistic regression analysis was used to evaluate the relationship between the quantitative pulmonary fibrosis score and the related risk factors in 248 COVID-19 patients. Their results showed (Table 2) that there were significant relationships between pulmonary fibrosis and the levels of albumin and IL-6, which suggests that IL-6 and albumin are independent risk factors affecting pulmonary fibrosis.

PATHOLOGY

In a systematic review of pathological findings in COVID-19 by Polak, S.B., Van Gool, I.C., Cohen, D. et al. using PRISMA-IPD guidelines, 42 articles reporting 198 individual cases were reviewed. In lung samples ($n=131$ cases), three main histological patterns were identified : *epithelial* ($n=110$, 85%), with reactive epithelial changes and DAD; *vascular* ($n=76$, 59%) with microvascular damage,

Table 1: FIBROGENIC MECHANISMS ASSOCIATED WITH VIRAL INFECTIONS

MECHANISM	SUMMARY
Viral activation of profibrotic pathways	-Altered renin-angiotensin system balance -Inhibition of host translation and altered cell cycle -Activation of growth factors (e.g., FGF, EGF, and TGF?)
Direct cellular injury	-Cytoskeletal rearrangement -Type II alveolar epithelial cells -Macrophages -Endothelial cells -ARDS -Immune Recruitment
Cytokine induced injury	-Neutrophil reactive oxygen species -Macrophage exosomes -Aberrant wound-healing response
Mechanical injury	-Volutrauma/ Atelectrauma -Barotrauma -Biotrauma
Age	-Altered cellular communication -Stem cell exhaustion -Extra cellular matrix dysregulation

Table 2 : Risk Factors for post Covid Fibrosis

Index	HR	95%CI	P value
Age(years)	1.001	0.975–1.027	0.941
High fever ($\geq 38.5^{\circ}\text{C}$)	0.502	0.174–1.450	0.203
Cough	0.708	0.309–1.621	0.708
Chest tightness	0.772	0.263–2.270	0.757
IL-6(acute stage)*	1.081	1.021–1.144	0.007
IL-6 (hospital discharge)	1.119	0.969–1.292	0.125
Lymphocyte $\times 10^9$ per L	0.921	0.711–1.194	0.536
Lymphocyte %	0.988	0.955–1.022	0.479
AST (U/L)	1.02	0.990–1.051	0.192
Albumin (g/L) *	0.821	0.734–0.918	0.001
PT (s)	0.93	0.822–1.052	0.250

(micro)thrombi, and acute fibrinous and organizing pneumonia; and *fibrotic* ($n=28$, 22%) with interstitial fibrosis.

Table 3-Findings on Gross Examination

FINDINGS	CASES
Increased Lung Weight	82(88%)
Diffusely congested and oedematous parenchyma	76(83%)
Haemorrhagic changes	20(22%)
Macroscopic Emboli	9(10%)

HISTOPATHOLOGY

Scored for the presence or absence of epithelial, vascular, and/or fibrotic patterns of lung.

1. EPITHELIAL PATTERN- In 110(88%), Interstitial inflammatory infiltrate:predominantly of lymphocytes and/or plasma cells. Intra-alveolar infiltrate:Macrophages.
2. VASCULAR PATTERN- Present in 76(59%). Microthrombi and proteinaceous and fibrinous exudates.
3. FIBROTIC PATTERN-Obsereved in 28 patients (22%). Typified by interstitial fibrosis.The presence of fibrosis (occurring separately or in combination with epithelial and/or vascular injury) was not associated with mechanical ventilation.

47 cases (60%) had two or more histological pattern, with the highest degree of overlap between the epithelial and vascular patterns (in 32cases).

Correlation with time-

Epithelial pattern of lung injury: Occurs early, may persist throughout the clinical course gradually declining by 28 days after the onset of symptoms

Vascular pattern: can occur early after the onset of symptoms

Fibrotic pattern: observed primarily three weeks from the onset of symptoms.

Three histological patterns can be present at different times but can also be present simultaneously.

NATURAL HISTORY OF POST COVID ILD (11-18)

More than 50 million people have already been infected by SARS CoV 2 globally. While the vast majority have mild or moderate infections, about 10% will develop severe COVID?19 pneumonia and 5% will develop ARDS, leaving a few million with significant pulmonary involvement. While the majority will resolve without residual lung damage, it is likely that a sizeable number will be left with residual fibrotic sequelae. Other influenza pneumonias, H1N1 is only occasionally complicated by fibrosis, whereas as many as 22% of patients with H7N9 pneumonia were left with fibrosis at 6 months.

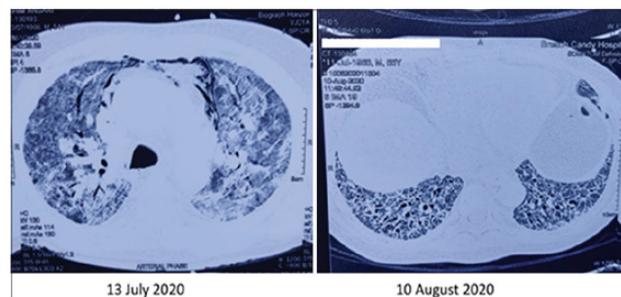
A study by Chang et al. in patients with SARS showed that when a second CT scan was repeated 4-6 months after the initial scan in patients with these two viral pneumonias, the parenchymal bands, traction bronchiectasis, and even honeycombing had regressed in significant numbers. Despite steroids now being the standard of care in most severely ill hospitalised COVID?19 patients, the usual doses most receive do not seem sufficient to prevent some of them being left with residual lung shadows.

A follow?up study by Zhao et al. of pulmonary function and radiology in 55 COVID?19 survivors 3 months after recovery showed that 71% had residual CT abnormalities, including evidence of interstitial thickening in 27%. Abnormal lung function (i.e., reduced diffusion capacity, restrictive abnormalities, and small airways obstruction) has also been identified at the time of discharge from the hospital and 2 weeks after discharge.

A prospective, multicenter, observational study of 86 severe SARS?CoV?2 survivors already under careful follow?up in Austria to evaluate the extent of cardiopulmonary damage. This was presented at the virtual European Respiratory Society (ERS) International Congress 2020. The preliminary prepublication findings reported at the European Respiratory Society (ERS) meeting this year found that the majority of patients were left with persisting dyspnea (37%), reduction in diffusion capacity (28%), and CT abnormalities (88%) at 6?week post-discharge. At 12 weeks, the CT abnormalities had dropped to 56%, from 8 points on the 6?week CT scans to 4 points on the 12?week scans. Their research is ongoing, and they expect to gather 24-week post-discharge results from more than 150 patients.

A study by Udwadia, et al. showed in contrast, the progression to PC?ILD in several of our patients. Figure 2 demonstrates a 45?year?old nonsmoker at one of their intensive care units (ICUs) with severe COVID?19 ARDS, who progressed within a period of 28 days to end?stage fibrotic lung disease, despite receiving remdesivir, tocilizumab, dexamethasone, and even 500 mg pulses of methylprednisolone.

Figure 2.TITLE



A retrospective analysis with follow?up imaging after a median of 11.6 days in 42 COVID?19 survivors by Xiong et al. showed evidence of progression in 83% with progressive opacifications, interstitial thickening, and fibrous strips being noted.

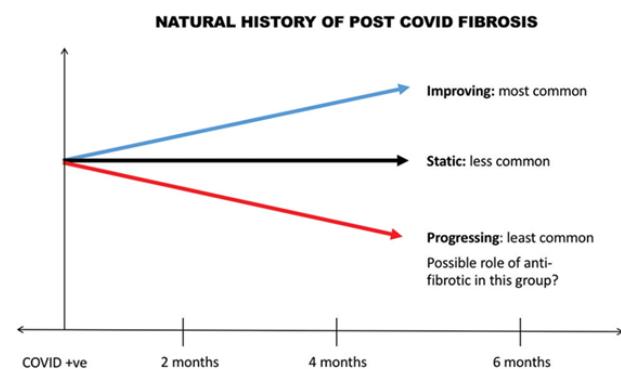


Figure 3

Changes seen on CT Scan may (Figure 3)- (1)persist, (2) gradually improve, or (3) even worsen with the passage of time. This has implications not only for patient prognosis but also for treatment. Antifibrotics may have an important role in those who progress but less if any role in the first two scenarios.

RADIOLOGICAL FINDINGS

M Sollini et al reported that radiological study of COVID-19 long-haulers has revealed an increase in [18F]FDG uptake which signifies persistent inflammation. These reports imply that unresolved inflammation may partly account for long-haul COVID-19 pathophysiology.

Chest imaging in different studies have shown persistent abnormalities. Liu, D., Zhang, W., Pan, F. et al. reported in a short term observational study in which a total of 149 patients who completed all CT scans were evaluated who were discharged

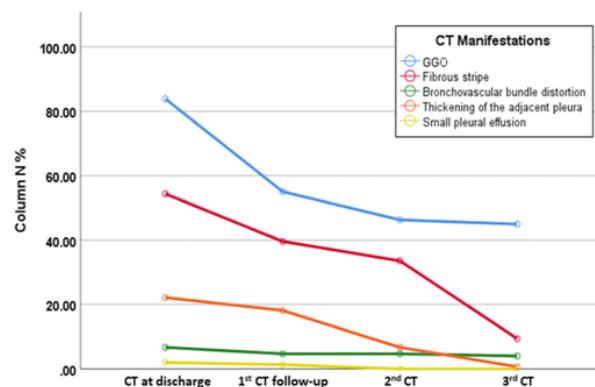
consecutively from the hospital between 5 February 2020 and 10 March 2020 and who underwent serial chest CT scans on schedule were enrolled. The radiological characteristics of all patients were collected and analysed. Afterwards, all patients underwent chest CT scans during the 1st, 2nd, and 3rd weeks after discharge.

Table 4: The cumulative percentage of complete radiological resolution at different time points -

	<i>n</i> = 149.
Chest CT at discharge	12 (8.1%)
The 1st CT follow-up	62 (41.6%)
The 2nd CT follow-up	75 (50.3%)
The 3rd CT follow-up	79 (53.0%)

Dynamic changes of chest CT manifestation in different time point after discharged (Figure 4). The predominant pattern was ground-glass opacity (GGO), fibrous stripe. With time, the positive count of GGO, fibrous stripe and thickening of the adjacent pleura gradually decreased, while GGO and fibrous stripe showed obvious resolution during the first week and the third week after discharge, respectively.

Figure 4



George PM, Barratt SL, et al. reported morphological pattern of lung disease on CT scan are regions of ground-glass opacification and consolidation, which variably comprise foci of oedema, organising pneumonia and diffuse alveolar damage.

The radiological changes in COVID-19 pneumonia do not appear to resolve fully in all patients and in some, inflammation matures to form fibrosis.?

Fig 5 A shows-Plain chest radiograph in a male patient with COVID-19 pneumonia referred for extracorporeal membrane oxygenation support.

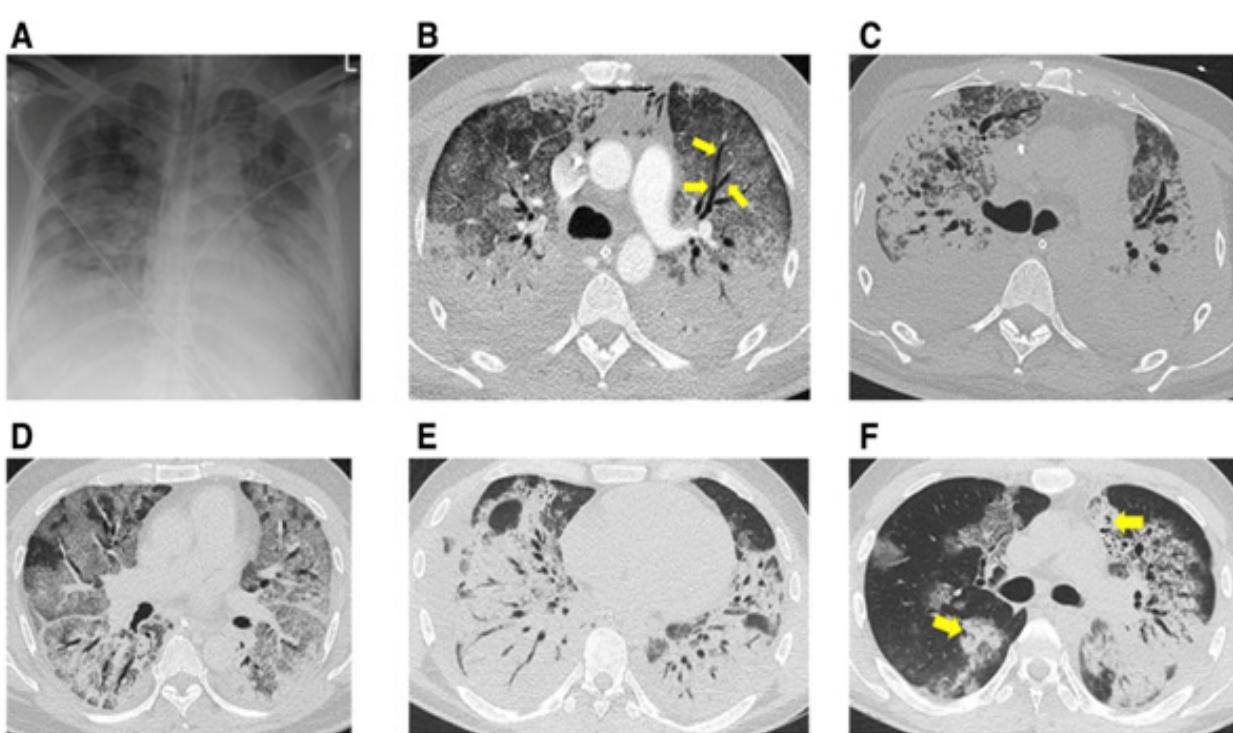


Figure 5 [A-F] Copyright © BMJ Publishing Group Ltd & British Thoracic Society. All rights reserved

Fig 5 B shows- CT images showing broadly symmetrical air space opacification with dependent dense parenchymal opacification and extensive ground-glass opacification with thickened interlobular and intralobular septa (the 'crazy-paving' pattern) in the non-dependent lung.

Fig 5 C shows -CT performed 10 days later again showing widespread air space opacification but now with 'varicose' dilatation (non-tapering) of airways in the left upper lobe indicative of developing pulmonary fibrosis.

Fig 5 D shows- Classical 'crazy paving' appearance in COVID-19. There is patchy but very extensive ground-glass opacification with superimposed fine thickening of interlobular and intralobular septa throughout both lungs.

Fig 5 E shows- A patient with COVID-19- related acute respiratory distress syndrome (ARDS) with image section though the lower zones showing characteristic findings of ARDS with symmetrical air space opacification but with a gradient of increasing density from the ventral to the dorsal lung.

Fig 5 F shows - Image just below the carina demonstrating foci of non-dependent consolidation (arrows), conceivably denoting areas of organising pneumonia.



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Fig 6 shows CT scan of an extubated survivor-a study performed during recovery (26 days after onset of COVID-19 pneumonia). During recovery (26 days after onset of COVID-19 pneumonia). Image section at the level of the carina demonstrating widespread ground-glass opacification and considerable architectural distortion. There is definite CT evidence of fibrosis-varicose dilatation ('traction bronchiectasis') of the anterior segmental bronchus in the right upper lobe (arrows).?

Zou J-N, Sun L, Wang B-R, Zou Y, Xu S, Ding Y-J, et al. published the characteristics and evolution of pulmonary fibrosis in COVID-19 patients as assessed by AI-assisted chest HRCT in 284 patients who were confirmed cases of COVID-19 and achieved a clinical cure from February 1 to March 31, 2020, at the Central Theater General Hospital of the Chinese People's Liberation Army. Follow-up studies on the evolution of pulmonary fibrosis were conducted with patients who returned to the hospital for chest HRCT reexaminations 30 days, 60 days and 90 days after hospital discharge.

Chest HRCT analysis - Quantitative scoring of pulmonary fibrosis was evaluated using the CT scoring method proposed by Camiciottoli. The scoring method had two parts, one for the lesion type and the other for the extend of the lesions. The maximum score was 30. The types of lesions were ground-glass opacities, linear opacities, interlobular septal thickening, reticulation, honeycombing and bronchiectasis, which were scored as 1, 2, 3, 4 and 5, respectively. The extent of each type of lesion was scored based on whether that lesion type was identified in 1 ~ 3, 4 ~ 9 or more than 9 pulmonary segments, which were scored as 1, 2 and 3, respectively. For example, if there were ground-glass opacities in 1 to 3 lung segments, the pulmonary fibrosis score was $1+1 = 2$. The total quantitative pulmonary fibrosis score was equal to the score for all types of lesions + the extent score for each type of lesion; the total score ranged from 0 to 30. Pulmonary fibrosis was classified into three groups based on the total score as follows: mild (0-10), moderate (11-20), and severe (21-30)

Table 5-The proportion of COVID-19 patients with pulmonary fibrosis at discharge and its relationship to the clinical classification.

Pulmonary fibrosis		Groups			Total
		Moderate COVID-19	Severe COVID-19	Critical COVID-19	
Yes	Mild ^a	101	10	3	114
	Moderate ^b	68	25	3	96
	Severe ^c	0	22	7	29
	Total	169	57	13	239
No	Total	45	0	0	45

The AI inflammation score-The AI inflammation score was determined based on the quantitative evaluation of lung inflammation by AI-assisted chest HRCT and was further used to analyse its relationship with the degree of pulmonary fibrosis.

The analysis revealed significant differences in the degree of pulmonary inflammation (PIV, PIV/WLV) and the extent of the affected area (the affected lung segments and lobes) among the three groups ($P<0.05$ or 0.01 , Fig 7). These results confirmed that there were significant differences in the extent and degree of lung inflammation among patients with mild, moderate and severe pulmonary fibrosis; that is, patients with severe pulmonary fibrosis had the most severe and extensive lung inflammation, followed by patients with moderate pulmonary fibrosis, while patients with mild pulmonary fibrosis had the least severe and extensive lung inflammation.

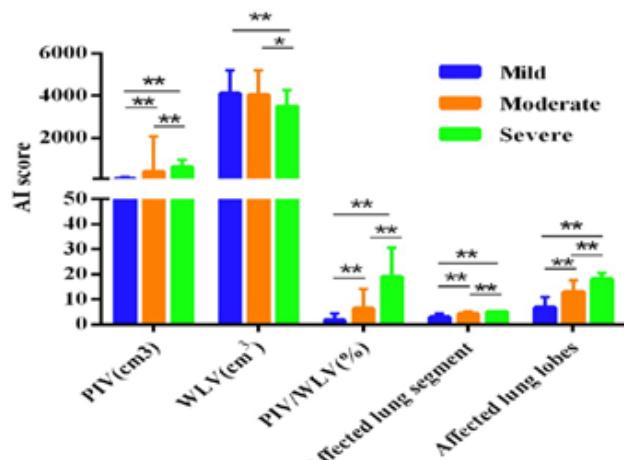
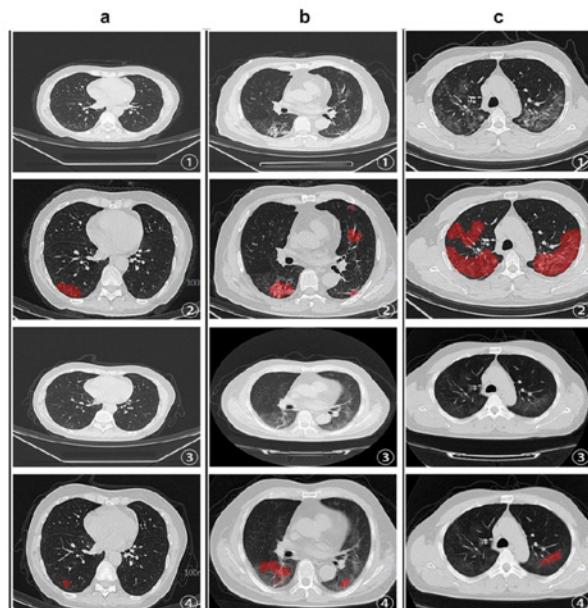


Figure 8 shows comparison of chest HRCT results between patients at discharge and 30 days after hospital discharge. a, b and c represent three separate patients:



a : represents a patient with mild pulmonary fibrosis,

b : represents a patient with moderate pulmonary fibrosis,

c : represents a patient with severe pulmonary fibrosis.

- represents the chest HRCT at discharge.
- represents the extent of lesions marked by AI at discharge (red);

- represents the chest HRCT 30 days after hospital discharge;
- represents the extent of lesions marked by AI 30 days after hospital discharge (red)

PREDICTORS FOR POST-COVID ILD AND FIBROSIS

A number of factors have been identified as predictors for Post-Covid ILD and fibrosis included advanced age, severe illness, prolonged ICU/hospital stay and mechanical ventilation, a history of smoking, and chronic alcoholism. The severity of the lung injury and the inflammatory response are known to correlate with the extent of fibroblastic response required to repair the injury. Higher levels of CRP and IL-6 during illness might lead to the formation of fibrosis during recovery. (Fig. 9)

TREATMENT FOR POST COVID FIBROSIS

- STEROIDS-Most patients who develop PC?ILD are hypoxic, and after the results of the RECOVERY trial were announced on June 16, steroids became the standard of care in hypoxic patients in ICUs across the world.that the doses of steroids recommended in COVID?19, in the acute stage, were modest doses of 4-6 mg dexamethasone for no more than 10 days. Despite most patients currently receiving steroids in equivalent or higher doses, steroids alone do not seem to be sufficient to prevent the development of fibrosis. Udwadia, et al.proposed that steroids

be continued on discharge if the CT scan prior to discharge continues to show significant GGOs and the patient remains hypoxic. At this stage caution against the use of large doses of oral steroids as they could worsen hyperglycemia and contribute to proximal myopathy which in turn would retard the patients' mobility and rehabilitation. They recommend using no more than 20-30 mg of prednisolone at discharge and tapering it on follow?up depending on the patient's response.

- ROLE OF ANTI-FIBROTIC AGENTS-Both COVID and IPF share many common demographic factors, disproportionately affecting males, the elderly, and smokers. Fibrosis with fibroblasts and honeycombing has clearly been demonstrated in autopsies and explanted lungs of patients with SARS?COV?2. For all these reasons, it is reasonable to assume that anti fibrotic drugs may have a potentially valuable role in this setting.

The excessive inflammatory state, associated with the presence of fibrotic tissue induced by SARS-CoV-2, has been shown to play a key role in clinical cases considered more critical.

In the more severe stages of viral infection, excessive release of pro-inflammatory mediators, such as cytokines, leads to lung damage with extensive fibrosis and rapid onset of respiratory distress syndrome.

Figure 9

Clinical and Lab predictors

- Levels of C-reactive protein
- Interleukin-6
- Longer-term of hospitalization
- Pulsed steroid therapy and antiviral therapy
- Tachypnoea

HRCT Imaging

- Interstitial thickening
- Irregular interface*
- Coarse reticular pattern and
- Parenchymal band*

Advanced disease

- More segments involved
- Larger lesion diameter manifested

* predicts the formation of pulmonary fibrosis early

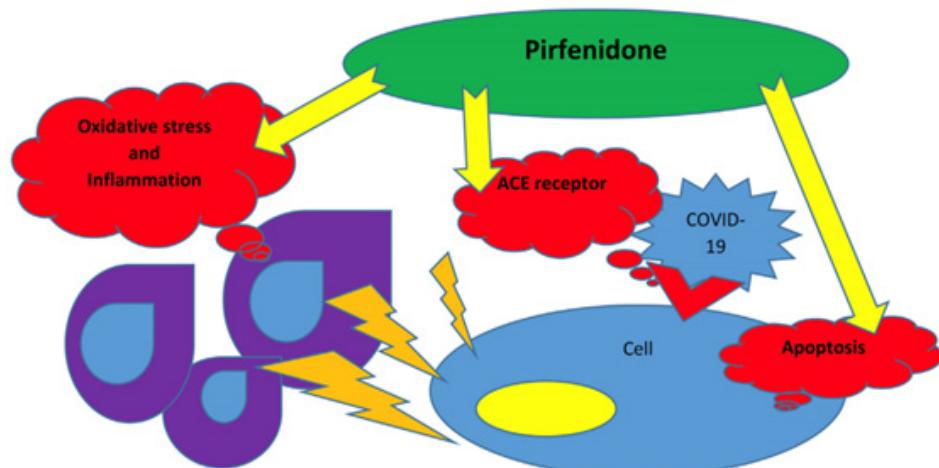
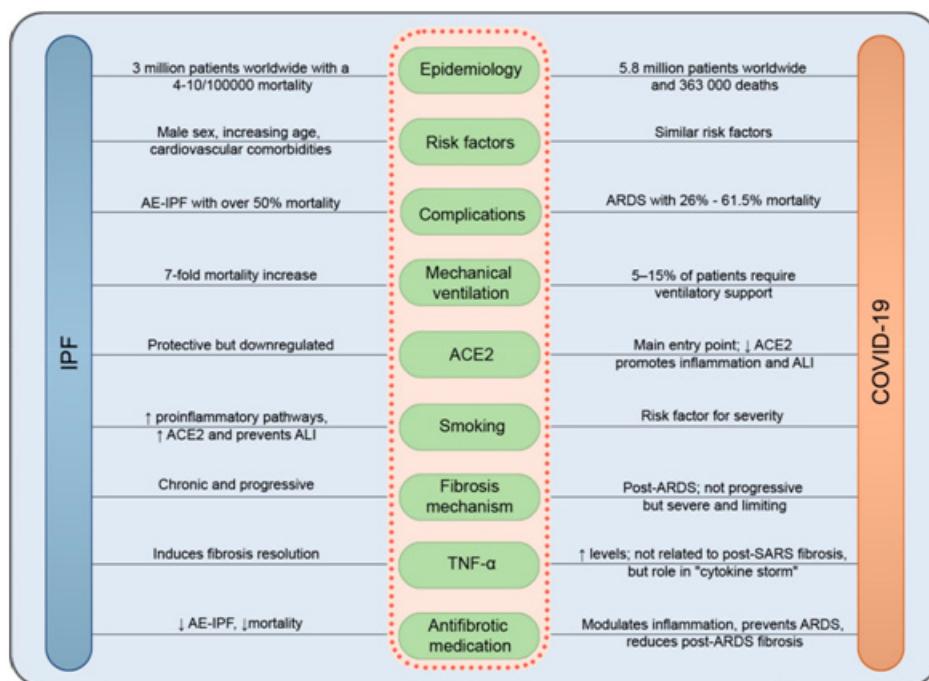


Figure 11 : Copyright of <https://doi.org/10.1016/j.mehy.2020.110005>

The use of agents to prevent or reduce fibrotic status, as pirfenidone, may be therapeutically effective in preventing serious or fatal complications. Pirfenidone is the drug of choice in the treatment of idiopathic pulmonary fibrosis (IPF) and with a pleiotropic mechanism of action reduces the fibrotic and inflammatory state of lung tissue.

PIRFENIDONE

1. Inhibits apoptosis.
2. Down regulates ACE receptor regulation.
3. Ameliorates oxidative stress.
4. Decreases inflammation.

Anti-inflammatory actions of Pirfenidone-

1. Inhibits TNF-? secretion and decrease a large number of other inflammatory cytokines.
2. Ameliorates lipopolysaccharide induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation

Anti fibrotic actions of pirfenidone-

1. Inhibits TGF- ?,Down-regulating of profibrotic gene expression and collagen secretion.
2. Collagen I fibril formation and causes a reduction in collagen fibril bundles.

- Pleiotropic actions- immune system and extracellular matrix (ECM); regulates tissue injury and repair

NINTEDANIB-

The arrow size indicates the degree of contribution to pulmonary fibrosis suggested by the published data. The dotted line indicates that very little data was available

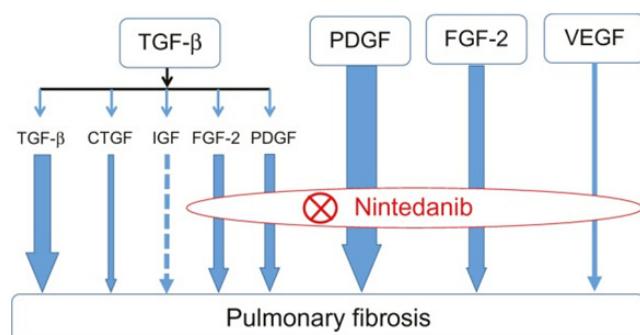


Figure 12

The profibrotic effects of TGF- β are mediated by several growth factors, including PDGF and FGF-2. Nintedanib improves pulmonary fibrosis by inhibiting the action of PDGF, FGF-2, and vascular endothelial growth factor, indicating indirect inhibitory effects on TGF- β signalling.

Nintedanib was also associated with shortened lengths on mechanical ventilation.

Kaplan-Meier curves for evaluation of 28-day mortality and length of mechanical ventilation. The solid black lines represent patients in the nintedanib group, and the dotted black lines represent patients

in the control group. Log rank test was conducted for 28-day mortality, and the Gehan-Breslow-Wilcoxon test was conducted for the length of mechanical ventilation to compare the curves between the groups.

3. NOVEL ANTIFIBROTIC THERAPIES

There has been an enormous increase in the number of compounds being assessed for the treatment of pulmonary fibrosis, many with effects on the immuno-inflammatory system. Indeed, a number of early anti-fibrotic studies focused on key antiviral proteins, such as IFN- β and IFN- γ . Subsequent studies have found that exogenously administered as well as endogenously produced interferon might induce pulmonary vasculopathy, and this finding is important given that pulmonary vascular disease could play an important role in severe COVID-19 disease. Indeed, circulating IFN- γ and CXCL10 concentrations are raised in patients with severe COVID-19.

CONCLUSION

A universally acceptable protocol for follow up a treatment for Post covid lung fibrosis is yet to be proposed. Treatment is being individually tailored based on the severity of the infection and other factors, with regular follow up, after a baseline for investigations including a HRCT chest, 6MWT, PFT is obtained.

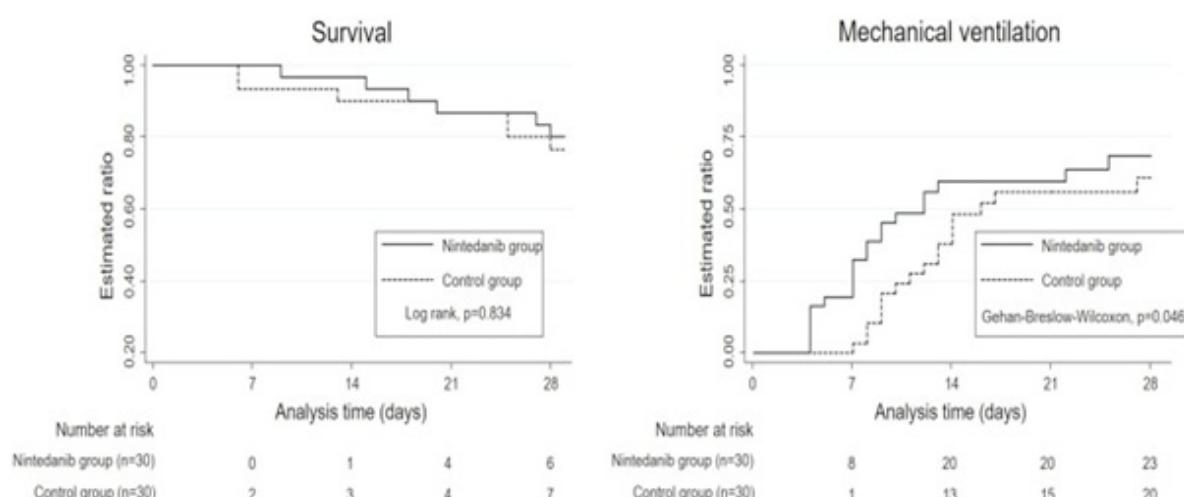


Figure 13

	Inhibits viral infection or disease	Inhibits experimental acute lung injury	Inhibits IL-1 or IL-1 effects	Inhibits IL-6
Nintedanib	Not described	Not described	Yes ^{38,39}	Yes ^{40,41}
Pirfenidone	Not described	Yes ⁴²	Yes ^{43,44}	Yes ⁴²
αvβ6 integrin blockers and knockout mice	Yes ^{45,46}	Yes ^{47,48}	Yes ⁴⁸	Yes ⁴⁹
Gal-3 inhibitor and knockout mice	Yes ^{50,51}	Yes ^{51,52}	Yes ⁵¹	Not described
Autotaxin inhibitor	Not described	Not described	Not described	Yes (skin), ⁵³ not described
Lysophosphatidic acid inhibitor (BMS-986020; SAR100842)	No	Yes ⁵⁴	Not described	Yes (skin) ⁵³
JNK inhibitor	Yes ⁵⁵⁻⁵⁸	Yes ⁵⁹	Not described	Yes
mTOR pathway modulator	Yes ⁶⁰	Yes ⁶¹	Yes ⁶¹	Yes ⁴³
SAP (also known as PTX2)	Yes ^{60,62,63}	Yes ⁶⁴	Not described	Not described
AT2R inhibitor	Not described	Yes ^{65,66}	No ⁴⁴	Yes ⁶⁵

Table: Potential link between antiviral mechanisms and antifibrotic drugs

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Phase and No. of patients	Study Title	Patient Population	Study Endpoints
Phase 2 N= 148 (2:1)	Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis COVID-19 (FIBRO-COVID) NCT04607928 Status: Recruiting	SARS-CoV2 infection with severe pneumonia and ARDS, with subsequent torpid recovery and/or incipient clinical-radiological signs of pulmonary fibrosis. HRCT with fibrotic radiological changes of at least 5% after recovery from the acute process (HRCT chest during the screening period, performed minimum after 1 month of the acute phase and maximum 90 days after hospital discharge) Pirfenidone vs Placebo	<u>Primary Endpoint (Time Frame 24 weeks)</u> • Change From Baseline in % in forced vital capacity (FVC) • Change From Baseline % fibrosis in high resolution computed tomography (HRCT) of the lung <u>Secondary Endpoint (Time Frame 24 weeks)</u> • Maintenance of stability or functional improvement FVC. Stability will be considered when the FVC does not > 10% or <10%; the DLCO >15% or <15%. % FVC >10% or in DLCO >15% will be considered significant improvement. • Decreased oxygen requirement for physical activity • Improved exercise capacity (> 50-meter improvement or less decrease in% oxygen saturation) • Hospitalizations • Visits to the Emergency or Day Hospital for respiratory causes • Lung transplantation • Death
N= 450	Short Term Low Dose Corticosteroids for Management of Post Covid-19 Pulmonary Fibrosis NCT04551781 Status: Completed	COVID-19 diagnosis with a positive nasopharyngeal swab, they were discharged from quarantine hospitals after 2 Polymerase chain reaction (PCR) swab negative for COVID-19, and have persistent radiological changes in follow-up chest computed tomography (CT) chest 20 Mg Prednisone for 14 days vs control group	<u>Primary Endpoint (Time Frame 14 days)</u> • resolution of CT chest infiltrates as evaluated by radiologist on a score of no infiltrates, <5%, 5-25%and >25 % infiltrates

SUMMARY OF VARIOUS TRIALS ON POST COVID LUNG FIBROSIS

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Among all the organ disease ramifications that can be caused by Covid-19, the cardiac involvement carries the most sinister significance apart from the lung disease. Prior heart disease is one of the most important risk factor for mortality in Covid19. Cardiac involvement worsens both the short term and long term prognosis. Cardiac involvement maybe caused by a direct viral effect, inflammation-induced thrombotic tendency, hypoxia and hypotension caused by severe Covid disease, drug-induced side effects, or a combination of these factors. Subclinical heart disease occurs in a huge proportion of patients with Covid19. Finally mRNA vaccines may cause myocarditis in some of the recipients. In this chapter, we aim to introduce the present concepts in the complex interplay between heart disease and Covid 19. It should be understood that a lot of future studies have to be done to understand this relation in a better detail.

Cardio vascular disease as comorbidity for covid-19 mortality:

A lot of studies have shown that the mortality rate is higher in patients with covid-19 with different comorbidities like age, hypertension, diabetes, obesity, cardiovascular disease, and renal disease. Among these comorbidities, it is the associated heart disease, which worsens the prognosis most significantly in these patients. The mortality rate of patients with COVID-19 with cardiovascular disease is much higher than in those with COVID-19 without cardiovascular disease (16.7 versus 4.7%)¹. In a meta-analysis² of 56 studies done by Hessami et al, acute cardiac injury, hypertension, heart failure arrhythmia, coronary artery disease and cardiovascular disease were significantly associated with mortality in Covid 19 patients. A lot of other studies demonstrated a similar high mortality rates in covid-19 patients with cardiovascular diseases^{3,4}.

There were slightly different results when a multivariate analysis was used. From a recent study⁵ using data from CAPACITY Covid registry and LEOSS study, the authors concluded that those admitted COVID-19 patients with preexisting heart disease were older, predominantly male and often had other comorbid conditions. The mortality was higher in patients with cardiac disease (29.7% versus 15.9%). However following multivariate adjustment this difference was not statistically significant. Associations with in-hospital mortality by heart disease subtypes varied considerably with the strongest association for heart failure, particularly for severe heart failure.

Covid19 as a cause of cardio-vascular disease:

There are several mechanisms through which cardiac disease can occur in the course of covid-19.

1. Demand supply mismatch of oxygen and nutrients causing myocardial injury leading to type-2 myocardial infarction:⁶ The oxygen levels fall in Covid-19 because of the ventilation perfusion mismatch in the lungs. The demand for the oxygen increases at the same time as the heart rate increases with fever, sepsis and with shock. In type-2 myocardial infarction, there is no acute coronary syndrome but the predominant cause is the reduction in oxygen supply in the face of an increase in demand, which will lead to the cardiac muscle injury resulting in an increase in troponin values.
2. Covid-19 leading to cytokine storm⁷: It is widely known that the major mechanism of tissue injury due to covid-19 is mediated through unbridled activation of various cytokines. The widespread production of pro-inflammatory cytokines shatters the

thrombotic homeostasis maintained by the endothelial tissue. This leads to thrombosis and local tissue injury. Pro-inflammatory cytokine molecules also lead to increase in the sympathetic nervous system activation, which will lead to vasospasm and further tissue damage.

3. Endothelial injury^{6,8} as a unifying mechanism of covid-19 induced pathology:

Endothelial dysfunction represents one of the most important mechanisms of covid-19 pathophysiology. The cardiac muscle damage may be caused by endothelial dysfunction leading to micro-vascular thrombosis in the coronary vasculature. Not only myocardial injury, but almost all the pathophysiological features of covid-19 can also be explained by the endothelial damage of various organs. The several organs that are affected by the covid-19 have endothelial dysfunction in common. The widespread thrombosis in the microvasculature observed in autopsy studies is most probably because of an endothelial dysfunction. Pre-existing endothelial damage mediated by hypertension, diabetes and obesity lead to worse outcomes in these subgroups of covid-19 patients.

Direct viral effects may also induce endothelial damage. This hypothesis is based on two important pieces of evidence. First, the endothelium has a lot of ACE 2 receptors through which the virus can enter the cells. Second, the Sars Cov 2 viral elements were demonstrated in the endothelium.

Apart from the direct viral assault, the endothelial involvement may also occur as a result of perivascular inflammation. The increased cytokines, which are pro-inflammatory will lead to perivascular inflammation in various organs and this in turn may damage the endothelium. Thus the cytokines and endothelium work in tandem to amplify inflammation, sympathetic nervous system activation and tissue damage, in presence of the viral stimulus. This results in

venous and arterial and micro-vascular thrombosis leading to myocardial damage when the endothelium of coronary microvasculature is involved.

Another purported mechanism of endothelial damage may be mediated by the vascular endothelial glycocalyx⁶ (VEGLX). High circulating levels of VEGLX components is associated with the worst prognosis in critically ill Covid patients.

4. Direct myocardial injury by Sars Cov 2 Virus:

Cardiac myocytes have a lot of ACE2 receptors allowing the entry of Sars Cov 2 virus directly into the myocardium. Thus direct myocardial injury is known with Covid19.

The different cardiac manifestations of Covid 19:

Arrhythmias: Atrial Fibrillation occurs in 1.8⁹ to 12.1% of the individuals. Atrial fibrillation is the most common tachyarrhythmia in Covid 19 patients.¹⁰ Patients with covid 19 and atrial fibrillation had worse prognosis, but in multivariate models, AF was not an independent risk factor for adverse events.¹¹ Patients with Atrial Fibrillation tend to have hemodynamic instability with fast ventricular rates. Prompt correction of rate or rhythm and proper anticoagulation are required in patients with atrial fibrillation.

Sinus tachycardia and sinus bradycardia are common in Covid 19 patients. Sinus tachycardia may be because of fever, anxiety, hypovolemia, and secondary infection or it may even indicate myocarditis. Sinus bradycardia may also indicate cardiac involvement, but is more frequently signals a self-limiting bradycardia.¹² Sinus bradycardia is a common side effect of Remdesivir injection as well. High grade AV block occurs in 0.5% of the patients and should be treated with temporary or permanent pacing.

Heart failure: This is a complication with grave prognosis. The incidence of heart failure in Covid-19 varies widely in different studies ranging from 1.6 to 33%. In a recent meta-analysis done by Zuin M et al, the course of covid-19 patients was

complicated by acute heart failure in 20.2% of cases¹³. The myocardial injury in some patients is self-limited but in others persistent inflammation could be detected in cardiac magnetic resonance and endocardial biopsy. There is an increased incidence of heart failure with preserved ejection fraction as well in patients with covid-19¹⁴. Heart failure patients are often associated with multiple comorbidities and have an increased risk of mortality. The clinical picture shows a worsening of breathing difficulty not correlating with inflammatory markers of covid-19. Orthopnea, an elevated jugular venous pressure, new onset third heart sound and basal rales may clinically indicate heart failure in these individuals. Prompt recognition of heart failure is important for management and missing this diagnosis may lead to a fatal outcome. Proning of patients in Covid-19 helps in the improvement of oxygenation, but those Covid-19 patients whose clinical course is complicated by heart failure may experience deterioration with prone position. Fluid balance is very important in all the patients with covid-19, but is critical in those complicated with heart failure. The early recognition of heart failure will help in starting the guideline-directed medical therapy, which helps in saving lives. Finally rhythm disturbances are more common in patients with a combined covid pneumonia and heart failure.

Pericarditis and myopericarditis: Confirmed myopericarditis is not very common in patients with Covid-19. In one study, 0.3% of covid patients are known to have this complication. Pericarditis in covid is usually associated with underlying myocarditis. Sometimes pericardial effusions can occur.

Myocardial injury and Troponin elevation: This is by far the most common cardiac complication seen in covid-19 patients. In various studies, the incidence was described between 7.2% and 36%^{15,16,17,18}. Troponin elevation can either be because of an ischemic myocardial injury or a non-ischemic myocardial injury. Ischemic myocardial injury occurs because of a coronary plaque rupture, erosion, coronary spasm, or endothelial injury leading to microthrombi. Non-ischemic troponin elevation is because of severe hypoxia, sepsis, cytokine storm, pulmonary embolism, tako-tsubo

like cardiomyopathy, or severe systemic inflammation. Sometimes, a troponin elevation may be caused by renal failure without myocardial injury and at other times, renal failure and myocardial injury may occur together to cause a troponin elevation.

Deep venous thrombosis and pulmonary embolism: Right heart failure and acute cor pulmonale may occur in covid-19 patients because of deep venous thrombosis followed by pulmonary embolism. Prolonged bed rest, inflammation, thromboembolic phenomena and viral induced endothelial dysfunction may all contribute to an increased incidence of pulmonary embolism in Covid pneumonia than in other patients of Acute Respiratory Distress Syndrome. In a study of Italian Covid patients by Fernando Scudiero et al¹⁹, Pulmonary embolism was noted in 14% of the patients admitted to the hospital. The authors also demonstrated a high risk of mortality among the patients who had pulmonary embolism during admission for Covid pneumonia. Pulmonary embolism has disastrous consequences in Covid pneumonia because of an interference with gaseous exchange and circulation thereby exacerbating the already worsened ventilation perfusion balance in Covid pneumonia. In a meta-analysis done by Nicolas Gallsteegui et al²⁰, the incidence of pulmonary embolism was much lower at 7.1% in all hospitalized patients and 13.7% in the patients admitted to ICU with covid pneumonia.

TakoTsubo Cardiomyopathy²¹: The cardiac apical ballooning syndrome with normal coronaries known as the TakoTsubo cardiomyopathy has been reported in several covid-19 case series. The stress associated with Covid 19, along with severe inflammation and a dysregulated autonomic nervous system may lead to Takotsubo cardiomyopathy. As takotsubo cardiomyopathy closely resembles an acute myocardial infarction, it is imperative to distinguish between these two entities as their management differs substantially. This can be done only after ruling out an obstructive coronary artery disease through a coronary angiography. Most cases of takotsubo cardiomyopathy resolve spontaneously and supportive treatment is the main stay of

management of these patients.

Acute myocardial infarction in Covid: The incidence of acute myocardial infarction in covid is between 1.1%²² and 8.9%²³. An increased risk of myocardial infarction and stroke was observed in a Swedish study²⁴. The incidence rate ratio for acute myocardial infarction was 8.44% for the first week according to that study.

The mystery of reduced heart disease in hospitals during covid pandemic: The hospital admissions because of heart diseases have fallen dramatically during the first two waves of COVID-19. The admissions for acute myocardial infarction as well as congestive heart failure also fell during the first two waves. There was a dramatic reduction in the number of invasive cardiac procedures that were done during the pandemic. Francisco Leyva et al²⁵ have reported 64% reduction in coronary artery bypass grafting and 28% reduction in percutaneous coronary intervention in England during the first wave of the covid pandemic. They also reported a 41% reduction in Transcatheter Aortic valve Replacement and an 83% reduction in ablation for Atrial Fibrillation. The hospitalization for acute MI fell by 27% and heart failure fell by 28% both reductions being statistically significant.

The pandemic also saw a steep decline in the diagnostic procedures performed for the detection of heart disease²⁶. The coronary angiography was reduced by 55%, trans thoracic echocardiography by 59% and stress testing was reduced by 78%. The same procedures were reduced further by an additional 22% in low-income countries.

Despite a decrease in admissions due to heart disease, the mortality due to heart disease has increased during the pandemic. In a recent study by Marwan Saad et al²⁷, the mortality among patients with ST elevation MI and Covid-19 was higher than among those patients with ST elevation MI without COVID-19 (15.2% vs 11.2%). The patients who had COVID-19 and in hospital MI had a very high mortality compared to those patients with in hospital MI without COVID-19.

Overall, the mortality due to heart disease and stroke has increased during the pandemic. In the United States heart disease and stroke deaths were higher

after the onset of COVID-19 pandemic, between the months of March and August 2020, relative to corresponding months in 2019²⁸. However the increase in mortality due to heart disease and stroke was much more pronounced in Black Hispanic and Asian populations.

There are several reasons attributed to this dramatic reduction in the hospitalizations for the heart diseases, the most important being that the heart disease patients were really afraid to come to the hospitals during the first two waves of the pandemic. Even in well-developed countries with minimal social restrictions during the pandemic exemplified by Sweden in the SWEDHEART study²⁹, roughly 20% of acute myocardial infarction patients expressed hesitancy to seek medical care during the pandemic. In a Danish study³⁰, a lower in hospital mortality was compensated by a higher out of the hospital mortality in patients with cardiovascular disease during the pandemic, again suggesting the reluctance of patients to come to the hospital despite having a life threatening heart disease.

Covid 19 in patients with adult congenital heart disease:

Initially it was believed that adults with congenital heart disease would fare badly with COVID-19. However, in a study of adult congenital heart disease patients with COVID-19³¹ the overall case fatality rate was 2.3% and this mortality rate was commensurate with the general population with COVID-19. Anatomical complexity of the underlying congenital heart disease did not appear to predict infection severity whereas the physiological stage of the disease as indicated by cyanosis and pulmonary hypertension predicted worse outcomes.

Asymptomatic heart disease following covid 19:

A high incidence of subclinical heart disease was observed in several studies following COVID-19 infection. Though initial studies showed a high rate of cardiac involvement, the later studies revealed less sinister findings. In a study of German patients³² recently recovered from COVID-19 infection, cardiac magnetic resonance imaging revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of the patients. However, in a study involving nearly 800

professional athletes³³ previously infected with Sars Cov2, who were tested as a part of return to play cardiac testing programme in accordance with American College of cardiology recommendations, only 0.5% had abnormal cardiac screening results. Another reassuring picture came up in a recent Netherlands study³⁴. This study evaluated children who recovered from mildly symptomatic Covid 19 with a cardiac magnetic resonance imaging 38 days after a positive Sars cov2 RTPCR test. The CMR in these patients did not show evidence of myocardial inflammation, fibrosis or functional cardiac impairment. 17% of these patients however had minimal pericardial effusion suggesting of underlying subclinical pericarditis.

Myocarditis following covid vaccination:

Several cases of myocarditis were reported following mRNA Covid-19 vaccinations. There are two types of mRNA COVID-19 vaccinations in the world as of now: Pfizer-BioNtech vaccine and Moderna vaccine. The cases of myocarditis following these vaccines are seen especially in young males. This complication is more common after the second dose and usually occurs within several days after vaccination. The patients of myocarditis following vaccination usually present with chest discomfort, breathing difficulty or palpitations. The patients with post- vaccination myocarditis and pericarditis respond well to treatment and usually recover completely.

While the exact incidence of myocarditis following mRNA vaccines is not known, a study based on military health system in the United States³⁵ had identified 23 myocarditis cases after the administration of 2.8 million doses of mRNA based vaccines. Israeli minister of health³⁶ reported 121 myocarditis cases occurring within the 30 days of a second dose of mRNA vaccine among 50,00,00 people suggesting a crude incidence rate of approximately 24 cases per million following a second dose.

A lot of questions regarding myocarditis still remain unanswered. The exact follow-up required after this complication, the changes in vaccination schedule which may reduce the incidence of myocarditis and the duration for which the people diagnosed with

myocarditis are advised rest are not yet known. Further studies may clarify these details.

Cardiac involvement in multisystem inflammatory syndrome in children:

Multisystem inflammatory syndrome in children usually occurs a few weeks after an acute Sars Cov 2 infection. It resembles Kawasaki disease and is perhaps caused by an inflammatory response to Sars Cov 2 infection. The syndrome is not very common but may become quite severe. The cardiac involvement is common in MIS –C and may include ventricular dysfunction, coronary artery dilatations or aneurysms similar to those seen in Kawasaki disease, rhythm and conduction abnormalities. Severe cases may present with cardiogenic shock requiring inotropic support, mechanical ventilation or even extracorporeal membrane oxygenation. The treatment usually includes intravenous immunoglobulins, steroids and other immune-modulator agents. Majority of children with MIS-C recover with early and appropriate treatment.

Cardiovascular effects of drugs used in Covid:

There are several drugs that are used in the treatment of COVID-19, which may have adverse impact on the cardiovascular system. For example, hydroxy-chloroquine that was used widely in the treatment of COVID-19 in the first and second waves may cause a prolonged QT interval and Torsades de pointes. This is especially true when hydroxy-chloroquine is combined with Azithromycin. Though usually the arrhythmic risk is more of a concern with the long-term usage of hydroxy-chloroquine, even short-term usage of this medication may cause QT prolongation and Torsades de pointes if there are underlying conditions like renal failure or dyselectrolytemia.

Remdesivir, which is the only US FDA approved anti-viral medication at the time of writing of this chapter, can cause hypotension; bradycardia, QT prolongation and T wave abnormality. The JAK kinase inhibitor Baricitinib is an immune-modulator used in the treatment of COVID-19. It may cause increased thrombotic tendency along with an increased risk of secondary infections. Similarly convalescent plasma therapy was also implicated in elevated thrombogenicity. Ritonavir, a component

in the new anti-covid oral medication Paxlovid, may cause hyperlipidemia. Dexamethasone and Methylprednisolone may cause fluid retention and electrolyte imbalances, both of which may adversely impact patients already in congestive heart failure.

Conclusion:

Cardiac involvement in Covid-19 and a pre-existing cardiac disease complicating Covid-19 are dangerous and can affect the prognosis adversely. Early diagnosis and proper treatment are most important measures to save the Covid patients who have a cardiac involvement. There are several lacunae in our present understanding of the heart disease complicating COVID-19. As new and better studies are published, the complex interplay between Covid 19 and cardiovascular system will further be elucidated.

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Abstract

Background: COVID-19 was initially considered a respiratory disease but the SARS-CoV-2 virus can lead to serious systemic consequences affecting major organs including the digestive system.

Summary: This review brings new clinically important information for the gastroenterologist. This includes: the mechanisms of tissue damage seen with the SARS-CoV-2 virus; the consequences of immunosuppression in patients with inflammatory bowel disease (IBD) and chronic liver disease with the additional risks of decompensation in patients with cirrhosis; the impact of COVID-19 on gastrointestinal emergencies, on gastrointestinal endoscopy, diagnosis and treatments. These highlight the need to understand the clinical pharmacology, toxicology and therapeutic implications of drugs commonly used by gastroenterologists and their links with COVID-19. Key Messages: Any part of the digestive system may be affected by the SARS-CoV-2 virus, and those with pre-existing disease are at greatest risk of adverse outcomes. The risk for drug-drug interactions is considerable in patients seriously ill with COVID-19 who often requires mechanical ventilation and life support. Some repurposed drugs used against SARS-CoV-2 can cause or aggravate some of the COVID-19-related gastrointestinal symptoms and can also induce liver injury. Ongoing clinical studies will hopefully identify effective drugs with a more favorable risk benefit ratio than many initially tried treatments.

Introduction

The pandemic caused by the novel SARS-CoV-2 virus has led to the disease now termed COVID-19 by the WHO [1]. This has been followed by an explosion of information about this novel virus much of which is important and clinically relevant

to gastroenterologists. COVID-19 was originally considered a respiratory disease but increasing evidence identified the potentially serious systemic consequences involving major organs, including those of the digestive system. This review brings together the salient information relating to the digestive system. SARS-CoV-2 is a single-stranded RNA virus, initially described as a serious acute respiratory virus of the coronavirus (SARS) family and is similar to those viruses which caused the 2002–2004 SARS epidemic, originating in China, and the 2012–2020 MERS outbreaks in the Middle East. COVID-19 is closely related to bat coronaviruses, suggesting COVID-19 has a similar zoonotic origin. The virus is highly contagious and spreads predominantly by respiratory droplets and aerosol while SARS-CoV-2 has been isolated from stool but faecal-oral spread has not been confirmed to date.

Symptoms and Clinical Presentations

The predominant symptoms of COVID-19 infection in one large UK series of more than 20,000 hospitalized patients were fever (71.6%), cough (68.9%) and shortness of breath (71.2%), which reflects the case definition [2]. Only 4.5% presented without symptoms at the time of admission. However, 3 other symptom clusters were recognized including firstly, myalgia, joint pain, headache and fatigue and secondly abdominal pain, nausea and vomiting and diarrhea. 29% of all patients reported these enteric symptoms, mostly in addition to the respiratory symptoms, and only 4% complained of enteric symptoms alone. Han et al. [3], from Wuhan, the epicenter of the global pandemic, describe a unique subgroup of 206 COVID-19 patients presenting to hospital, 48 (23%) with one or more of only digestive symptoms of diarrhea, nausea and vomiting. The symptoms of anosmia and dysgeusia were added to the core symptoms of COVID-19. It is probable that these symptoms result from COVID-

19 neuropathy with a point of entry being by way of angiotensin-converting enzyme 2 (ACE 2)-expressing cells in the olfactory epithelium and reaching the olfactory bulb via axons extending to the olfactory nucleus in the pyriform cortex. The SARS-CoV-2 virus has remained positive in stools even after respiratory tract specimens were negative for the virus. The viral activity and replication in the gut persisted even after respiratory tract clearance of the virus. Such findings continue to support the concerns for feco-oral spread of COVID-19 although this has not been confirmed to date. These studies suggest that GI symptoms are frequently seen in patients with COVID-19, although respiratory symptoms remain the predominant presentation.

Pathogenesis

The pathogenesis of SARS-CoV-2 is now increasingly well understood, and serious disease outcomes are dependent on the ability of the virus to bind to the ACE 2 receptor which facilitates entry into epithelial cells. This can lead in the lungs to a severe host hyperimmune response with a life-threatening cytokine storm resulting in the systemic inflammatory response syndrome [4]. Virus entry into epithelial cells is achieved by way of the spike protein on the viral coat, which is primed by the cellular transmembrane serine protease 2 (TMPRSS-

2) (Figure 1).

In the gastrointestinal tract the mechanism is similar, and evidence for infection by SARS-CoV-2 has come from hospitalized patients who tested positive for the virus in stool. The ACE 2 receptor stained positive in the cytoplasm of GI epithelial cells, and staining for the viral nucleocapsid protein was present in the cytoplasm of gastric, duodenal and rectal glandular epithelial cells although not in esophageal epithelium. In inflammatory bowel disease (IBD), age, inflammation and disease location are critical determinants of intestinal expression of ACE 2 disease.

COVID-19 pandemic and Inflammatory Bowel Disease (IBD)

The onset of the COVID-19 pandemic has had a dramatic and immediate impact in the field of IBD, affecting the daily lives of patients, careers, health care professionals, and the research and academic community. Clinical practice has required basic redesign and re-evaluation of fundamental principles involved in patient management.

Inevitably, the first and overriding concern was to protect the safety of patients with IBD and their health care professionals and careers. Anxieties have been heightened by the widespread use of immune-

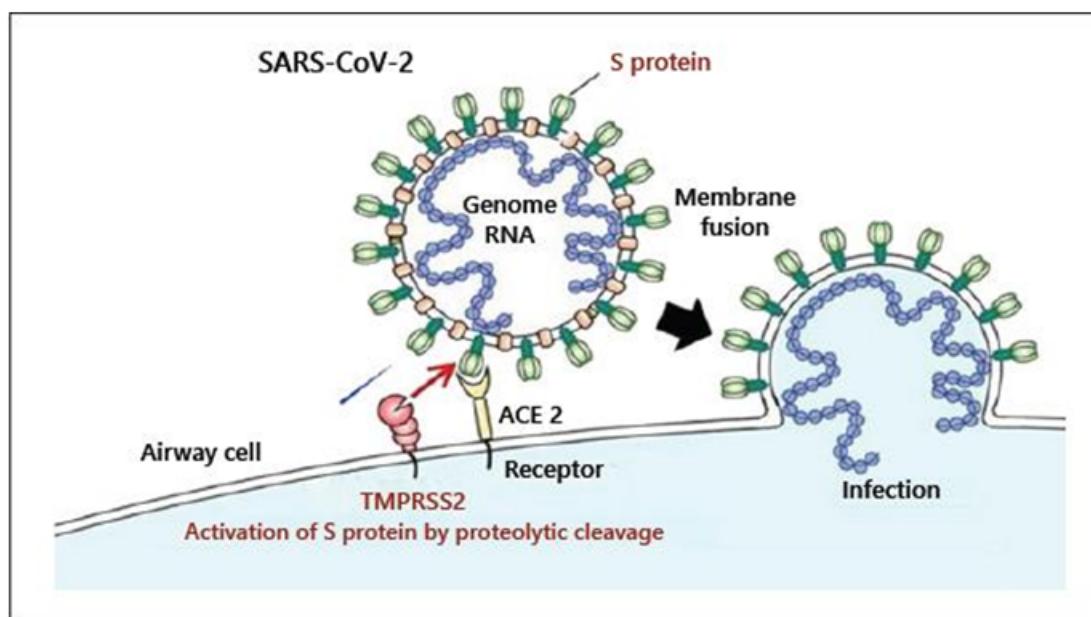


Figure 1: The dynamics of viral entry into human cells. Spike proteins on the surface of the SARS-CoV-2 bind to angiotensin converting enzyme 2 (ACE 2) receptors on the surface of the target cell while the type II transmembrane serine protease (TMPRSS2) binds to and cleaves the ACE 2 receptor. In the process, the spike protein is activated. Cleaved ACE 2 and activated spike protein facilitate viral entry, leading to infection.

modulator and biological agents in Crohn's disease and Ulcerative colitis, when treatment goals now involve full remission and mucosal healing. A consensus was issued by various International IBD societies on the key issues. It was widely held that continuing immune-active therapies, with strict attention to disinfection measures, social distancing and shielding where necessary, would be preferable to (indefinite) drug discontinuation, and the significant associated risk of relapse, the latter requiring investigation, hospital attendance and potentially more aggressive drug therapy or surgery [5].

Broadly, a consensus emerges that mortality rates are not unduly increased in IBD compared with the populations studied, but advanced age, comorbid illness and active IBD, particularly colonic disease, are key concerns within this patient population. Stopping immune-modulation and biological agents in this setting was considered necessary early in the pandemic and was associated with very low rates of COVID-19, but follow-up data confirm that stopping these agents has already been associated with significant problems related to the management of disease relapse.

Until more data are presented, it seems appropriate to advocate early and careful strategies for detection and treatment of active disease, limiting steroids if possible, using monotherapy with biological agents rather than combination therapy and otherwise observing conventional guidelines for drug management. During the height of the pandemic, elective and emergency surgeries were associated with high complication rates, highlighting the need for targeted and effective medical interventions.

New issues are surfacing in defining new parameters for resumption of "normal" life. For patients who have been in quarantine, there are inevitable concerns regarding socialization and re-integration, which require to be sensitively addressed. Telephone and video consultations have become popular among patients, clinicians and health care providers, as have strategies for telemonitoring. The need for non-invasive point-of-care testing is apparent with associated research in biomarker discovery.

COVID-19 pandemic and Liver Diseases

Early reports of COVID-19 described frequent

derangements of liver chemistry together with a correlation between changes and disease severity, so raising concerns of direct hepatic injury [7]. Most prominent were elevations of serum transaminase activity, with mild jaundice in a minority but only very few patients developing impaired synthetic function. RNA is present in the livers of COVID-19 patients; histological findings were primarily consistent with shock liver or pre-existing liver disease. It has been suggested that the histological changes reported in early severe cases are in fact best explained by the effects of a cytokine storm. Elevated liver chemistries are common at presentation and during COVID-19. The severity of elevated liver chemistries correlates with the outcome of COVID-19. The presence of CLD does not alter the outcome of COVID-19 [8]. Whether patients with pre-existing chronic liver disease (CLD) with COVID-19 present with a different clinical syndrome from those without CLD remains unclear. Symptoms reported to date appear broadly consistent, although perhaps with more prominent gastrointestinal involvement in CLD. Outcome data in CLD patients with SARS-CoV-2 infection are still being collected but appear to indicate a greatly increased risk of death, and that this risk increases with severity of liver disease such as increased Child-Turcotte-Pugh class or model for end stage liver disease. A key challenge in interpreting such studies is, however, accounting for concurrent risk from comorbidities such as obesity and other metabolic factors, and also in accounting for the correlations between cirrhosis and other major risk factors for COVID-19 outcome.

The effects of the SARS-CoV-2 pandemic on health care provision are wide-ranging and likely to affect the care of patients with CLD with, as yet, unquantified effects on hepatocellular carcinoma surveillance, esophageal variceal surveillance, viral hepatitis care, and immunosuppressive treatment regimens (e.g., greater use of budesonide in preference to prednis(ol)one) for patients with autoimmune disease. Further, increased alcohol consumption, drug use and rates of obesity are forecast following the epidemic and may be predicted to fuel the development of further CLD. Reductions in organ availability, pressure on intensive care beds and altered prioritization schedules have already affected those CLD patients awaiting transplantation.

Reactivation of chronic hepatitis B with dexamethasone therapy must be considered, especially where the virus is endemic. The reported benefit from corticosteroid therapy highlights the uncertainty regarding the relative risk of COVID-19 to CLD patients requiring immunosuppression, particularly those with autoimmune hepatitis, where data to guide care are urgently needed.

Management of immunosuppressive therapy and drug-drug interactions (DDIs) in patients with a history of liver transplantation, infected with COVID-19, must be balanced to permit an adequate immune response whilst avoiding rejection. Reducing immunosuppression to the most acceptable has been proposed, especially in the setting of lymphopenia or worsening infection, although evidence to guide such dose adjustments is lacking and, indeed, routine reduction is currently advised against by major guidelines.

COVID-19 is negatively affecting patients with liver malignancies. From the perspective of the liver, SARS-CoV-2 seems to be primarily of indirect concern: evidence for direct injury to the liver is limited but those with advanced cirrhosis appear at risk of decompensation and death from the systemic response seen in COVID-19; the indirect effects of the pandemic seem likely to have major effects on liver patients in impeding standard clinical care and in creating conditions conducive to the development of additional CLD.

COVID-19 infection and the Upper Gastrointestinal Tract

Early reports from China, all based on retrospective data, reported the prevalence of GI symptoms in COVID-19 cases between 11.4 and 50% [9]. GI symptoms presenting as an initial symptom cluster of COVID-19 infection has been reported in 3 up to 10% of adult patients and more frequently in children. Although upper GI symptoms are frequently present, the most serious GI symptom in the context of COVID-19 is severe diarrhea. Esophageal symptoms directly associated with the SARS-CoV-2 infection are not reported but heartburn is frequent, as in the general population and requires a standard approach with proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs). The observation of an apparent clinical benefit with famotidine in COVID-19 patients, who were taking

the drug for acid-related reflux, prompted a small study which reported an improved clinical outcome in COVID-19 patients. Upper GI tract symptoms may include loss of appetite (anorexia), nausea, and vomiting and/or abdominal pain. Anorexia is the most frequently reported symptom, although it is quite non-specific. Among the mechanisms considered are the systemic inflammation and malaise (fatigue) associated with the SARS-CoV-2 infection and also the need for various medications, which may include analgesics, antipyretics, antibiotics etc. (see below). Neurosensory effects such as dysgeusia and anosmia are often reported in patients with a mild clinical course and may contribute to diminished appetite and even nausea. So, although direct viral damage is thought to occur primarily in the small and large bowel, it does not exclude an origin for abdominal symptoms referred to the upper GI tract. In the absence of prospective endoscopy-based studies, reliable data on peptic ulcer prevalence and complications are not available. Endoscopy should be reserved for patients with bleeding or emergencies. Medical management of dyspeptic symptoms should rely on standard treatments.

Pancreatic Disease and COVID-19 infection

The point prevalence of SARS-CoV-2 infection presenting as acute pancreatitis is 0.27% among patients hospitalized with COVID-19. Idiopathic pancreatitis was the most common etiology in this group (69%) compared to 21% in patients who were COVID-19 negative. In a small clinical series of patients with COVID-19 pneumonia, pancreatic injury with mild clinical manifestation was detected in 9 of 52 patients (17%). In these patients, the authors noted a higher incidence of loss of appetite and diarrhea with increased pancreatic serum enzyme elevation, which they interpreted as pancreatic injury.

Among postulated mechanisms responsible for the induction of mild pancreatic injury, a direct cytotoxic viral involvement is possible since the expression of ACE 2 receptors in the pancreas, and particularly in pancreatic islets, has previously been described in the context of SARSCoV-2 infection. The TMPRSS2 and ACE 2 receptor, which together facilitate cell entry of the virus, were found on pancreatic ductular cells but causality is unproven. Reports are there to suggest either overweight or obese with atypical,

acute but proven pancreatitis in the context of a SARS-CoV-2 infection. The pattern of pancreatic inflammation was unusual with mild pancreatic edema but without peripancreatic necrosis, and with distinct duodenal/periduodenal inflammation accompanied by a profound systemic inflammatory response [10]. Studies have shown that COVID-19-associated acute pancreatitis is more frequently related to the severe systemic disease and multi-organ complications rather than directly by the virus.

GI Emergencies in COVID-19 Patients

GI emergencies during the COVID-19 pandemic represent a challenge in clinical practice. Diarrhea is the most common GI symptom associated with COVID-19 but it is usually mild. However, some patients report severe diarrhea with electrolyte disturbances or bloody, inflammatory diarrhea during or before onset of pulmonary symptoms.

Patients with severe COVID-19 were more likely to have gastrointestinal symptoms, especially abdominal pain, which often requires emergency consultation. Among the differing causes, some cases of acute pancreatitis have been reported to be primarily induced by the SARS-CoV-2 virus. There are several reports of acute cholecystitis.

GI bleeding is one of the most frequent reasons for emergency consultation. During the pandemic outbreak of SARS-CoV-2 virus, GI bleeding requiring the presence of a GI specialist can occur in patients suffering from COVID-19, but also in patients not suffering from this infection. GI bleeding in patients with COVID-19 is not as frequent as other GI symptoms.

The cause of the bleeding is often not identified, since endoscopic procedures are not always performed, and patients are managed conservatively with high-dose PPIs. When an upper GI endoscopy was performed, GI mucosal herpetic-like erosions and ulcers with biopsies testing positive for the SARS-CoV-2 virus have been reported. In 24 upper GI endoscopic procedures performed in patients with COVID-19 in one study, 75% had lesions including esophagitis (20.8%), duodenal ulcer (20.8%), erosive gastritis (16.6%), neoplasm (8.3%) and Mallory Weiss tear (4.1%), but no data on the indication for performing the endoscopic procedures were given.

Lower GI bleeding may also require emergency consultation and is being reported in association with COVID-19. One study, from Italy, showed a high proportion of lesions in patients with COVID-19 who underwent colonoscopy (the reason for the procedure was not specified), including segmental colitis associated with diverticulosis (25%), hemorrhagic ulcerative colitis (5%) and ischemic colitis (20%). An ischemic cause of GI bleeding in COVID-19 patients was confirmed in other case reports attributed to SARS-CoV-2 infection, after other etiologies for hemorrhagic colitis had been excluded. The ischemic etiology of these bleeding lesions has been attributed to a thrombotic dysfunction, due to excessive inflammation, a hypoperfusion state or even a direct inflammatory effect on the GI mucosa. The increased levels of D-dimer and fibrinogen found in many patients with COVID-19 may underlie not only the frequent peripheral and pulmonary thrombosis, but of the intestinal hypercoagulable state leading to ischemic events.

As a prophylactic therapeutic measure, PPI treatment is more effective than H2RA in the prevention of stress ulcer and upper GI bleeding with a similar risk of nosocomial pneumonia. Conversely, other common GI emergencies not linked to the SARS-CoV-2 virus still can occur during the pandemic.

In order to reduce, mitigate and control the COVID-19 pandemic and optimize resources, health care systems and GI units in particular have restructured their daily operations and activity. This has obligated medical teams to define which procedures could be deferred or performed based on their medical urgency taking account of the COVID-19 and procedural risks of spreading the disease and the expected outcomes for the patient. These procedures include diagnostic or therapeutic upper and lower endoscopy, their indication and the availability of appropriate personal protection equipment.

Endoscopic and Other GI Interventions in COVID-19 patients

The large number of COVID-19 cases has led to radical changes in endoscopy services as clinicians have tried to continue offering patients what are often life-saving services during this airborne viral pandemic.

Upper GI endoscopy procedures with open suctioning, including endoscopic retrograde cholangiopancreatography, endoscopic ultrasound and transnasal endoscopy, are considered aerosol-generating procedures (AGPs). The virus-carrying aerosols are not well blocked by the use of standard surgical masks, and all guidelines currently recommend the use of personal protective equipment (PPE) for such procedures including FFP3 masks, visors, head coverings, long-sleeved fluid-resistant gowns, two pairs of gloves and shoe coverings or cleanable shoes [11]. Addition of safety measures in endoscopy leads to low risk of transmission among health care professionals [12]. It is time consuming to put on, "don," and remove, "doff," the latter being especially critical to do in the correct safe sequence to avoid infection from the PPE itself. It is also hot and unpleasant to work in PPE, and it severely impedes communication between team members, with sessions usually lasting for a maximum 2–3 h.

Lower GI endoscopy may also be aerosol generating, but different groups have viewed this risk differently. Viral RNA is detectable in stool and has been detected even in sewage plants, but it is unclear whether this translates into viable virus. There is some evidence that colonic fluid rapidly inactivates viral particles, and early small studies did not detect viable virus; however, one study looking at those with a detectable viral RNA stool load did isolate viable virus in 2 of 3 patients. Therefore, lower GI endoscopy may have a substantially lower risk of passing on infection.

Endoscopy units also need to adapt to the pandemic, with the development of "cold" or "COVID-minimized" facilities being recommended which actively seek to exclude COVID-19 by telephone triage of all patients 5–7 days before appointment and nasopharyngeal PCR swabs 48–72 h before the procedure. Units need to arrange for social distancing avoiding build-ups in reception, recovery or discharge areas, ideally a linear flow through the unit to avoid patient pathways crossing and sufficient time between procedures for aerosols to settle, depending on room air exchanges, and for appropriate levels of endoscopy suite cleaning between cases. Units should separate "cold" elective work from "hot" emergency work where the patient is either known to have COVID-19 or there is

insufficient time to establish COVID-19 status. In some areas which did not have a significant viral peak and still have low prevalence, far fewer measures have been required, and endoscopy has been minimally interrupted and indicates what might be achieved by a reappraisal of the services and introduction of strategies of mitigation.

Despite the development of COVID-19-minimized facilities, patients have been reluctant to attend hospitals for medical emergencies or in cases where they are at high risk of a serious adverse medical outcome. It is critical that we develop mechanisms to find a way to deliver risk messages that allow patients to make rational decisions about their optimal care at a time of high anxiety generated by the press and social media. Emergency endoscopy for GI bleeding, bolus obstruction and cholangitis has largely continued, but we need to risk stratify elective patients as endoscopy services resume so that those at highest risk receive endoscopy first. For upper GI endoscopy biomarkers are less well established, but there is a need to avoid doing low-yield endoscopy, for example, dyspepsia without alarm features or simple reflux responding to PPIs. It seems likely in the post-COVID-19 era that endoscopy will be increasingly driven by pre-endoscopy biomarkers with expected higher rates of advanced imaging and therapeutic procedures per case, leading to "precision endoscopy."

Pharmacotherapeutic Considerations for GI drugs in COVID-19 patients

In this final section we highlight the impact of SARS-CoV-2 infection and its treatments on the management of GI and liver diseases. Some repurposed drugs against SARS-CoV-2 such as antivirals, especially lopinavir-ritonavir combinations, antimalarials and antimicrobials can induce diarrhea, nausea and also vomiting. Since drug discontinuation is not always possible, antidiarrheal compounds must be given to prevent dehydration and electrolyte disturbances. However, to avoid delaying viral clearance, antisecretory compounds (e.g., racecadotril) should be preferred to combination (antisecretory and antimotility) agents like loperamide. Similarly, nausea and vomiting need treatment to prevent dehydration and avoid interference with non-invasive ventilation, when needed. Anti-emetics should be used with caution since these drugs prolong the QTc interval,

especially when combined with other drugs being used for COVID-19 such as chloroquine, hydroxychloroquine and azithromycin. The gut-lung axis is bidirectional, and endotoxins and microbial metabolites can impact the lung through the bloodstream and, when lung inflammation occurs, it can affect the gut microbiota. Several studies show that respiratory viral infections are associated with a change in the intestinal microecology. Compared with controls, COVID-19 patients show significant alterations in fecal microbiota, with enrichment of opportunistic pathogens and depletion of beneficial commensals including Lactobacilli and Bifidobacteria, on admission and during hospitalization. Depleted symbionts and gut dysbiosis persisted even after clearance of SARS-CoV-2 and resolution of respiratory symptoms. Probiotics with anti-inflammatory effects could be useful to restore the intestinal microecology and prevent secondary bacterial infection in patients with COVID-19. Patients with IBD and GI cancer represent a challenge for gastroenterologists and oncologists with patients on immune-modulating treatments and biological and/or cytotoxic drugs. Corticosteroids and mesalazine are risk factors for severe COVID-19 among IBD patients, but this is not the case for TNF antagonists, such as infliximab which seems useful to treat both the underlying inflammation and SARS-CoV-2 pneumonia by countering the cytokine storm.

Cancer patients may be immunocompromised due to their underlying malignancy or anticancer therapy and carry multiple risk factors, placing them at higher risk of developing infections. Compared to the general population, the increased risk of contracting SARS-CoV-2 is estimated to be twofold. For GI cancer patients, limiting the risk of infection without compromising the treatment of the cancer should be the goal. Whenever possible, surgery should be postponed during the epidemic and oral chemotherapy should be favoured. When needed, radiotherapy should follow the RADS principle (remote visits, avoid radiation, defer radiation, shorten radiation).

Overt GI bleeding calls for endoscopic evaluation but during the pandemic urgent procedures were often deferred, giving priority to aggressive medical management. For both peptic lesions (which are

observed in 75% of upper GI endoscopies) and upper GI bleeding, PPIs are indicated (oral or intravenously, respectively), but, taking into account the many cotreatments in COVID-19 patients and the fear of DDIs, compounds with little or no interaction with CYP 450 (pantoprazole or rabeprazole) should be preferred. Because of the coagulopathy driven by SARS-CoV-2 infection, patients are often treated with medium or high-dose anticoagulants. NSAIDs and single or dual antiplatelet therapy are all risk factors for upper GI bleeding and pose additional risk when given concomitantly with anticoagulation. In this setting, PPI use is preferable to prevent development of gastric ulcers. Taken together, it has been suggested that PPIs could have a therapeutic role in the treatment of COVID-19. Some preliminary evidence of PPI benefits in the prevention of viral infections exists from a randomized trial where lansoprazole was associated with a reduction of frequency of the common cold and COPD exacerbation, thus attenuating the chance of contracting a viral infection.

Summary and Conclusions

The SARS-CoV-2 virus may lead to significant systemic disease and involve the GI tract, liver, biliary tract and pancreas by mechanisms involving cell entry by the ACE 2 receptor and TMPRSS2, which are dysregulated. In IBD clinical studies and registry data show that age, the presence of comorbidities and active disease are associated with increased adverse outcomes. SARS-CoV-2 infection does not appear to have significant direct hepatotoxicity but is associated with increased mortality in those with cirrhosis, by increasing the risks of decompensation. Upper GI tract symptoms are frequently reported in COVID-19 patients, most frequently anorexia and nausea; however, the expression of ACE 2 receptors is significantly lower in the esophagus and stomach than the lower intestines.

Acute pancreatitis does not appear to be causally related to SARS-CoV-2 infection although pancreatic enzyme abnormalities are not infrequent, most likely as a non-specific consequence of severe illness and the use of extensive medications, but a direct viral effect has not been excluded.

GI bleeding in patients with COVID-19 is not as frequent as might be expected, and the cause of

the bleeding is often not found, because endoscopic procedures are not always performed and patients are managed conservatively. Herpetic-like lesions in the upper GI tract and ischemic lesions attributed to a hypercoagulability syndrome and thrombotic events in the colon have been reported.

Endoscopy can be carried out safely in a COVID-19 environment with appropriate PPE and the establishment of new safe protocols. A decrease in the number of GI emergency endoscopic procedures has been linked to a reduction in the number of patients seeking medical attention during the pandemic as well as a reduction in the number of procedures performed because of the complexities mentioned. The use of some medications for managing COVID-19 may be associated with GI symptoms, and others may lead to serious adverse events or DDIs. The risks of immune-modulatory therapies in patients with IBD or CLD continue to be carefully studied but withdrawal of treatment in patients in remission is not advocated in view of the real and significant risks of relapse.

There is much research which is ongoing and questions still to be addressed to best guide clinical gastroenterologists through their daily practice.

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Covid -19 pandemic, caused by SARS-CoV2 viral infection was initially detected from Wuhan and has spread dramatically across all countries in the world. The impact is huge with the virus affecting more than 2.25 billion people and causing more than 4.5 million deaths. The mutative capacity of the virus and the emergence of variants have caused concern about tackling the disease and finding a universally effective vaccine and therapy. (1)

SARS-CoV 2 virus can affect many cells and tissues in the body. The most common is the respiratory system, leading to pneumonia and acute respiratory distress syndrome. The virus can involve other systems such as kidney, myocardium, liver and the brain, although comparatively in fewer patients.

Neurological manifestations of Covid-19 may be either due to a direct invasion of the brain tissue, resulting in anosmia/ ageusia, headache, myositis, encephalitis, etc., by the virus or as a secondary outcome due to hypercoagulable state (stroke) or secondary to an autoimmune process (Guillain Barre syndrome, acute disseminated encephalomyelitis).

Incidence : The incidence of neurological manifestations seem to vary from 12-85% based on different studies from different countries.(2) The variations in the incidence rate may be due to differences in the study design -prospective/ retrospective, duration of follow up etc. In a retrospective evaluation in approximate 11000 patients with Covid 19 from Phillipines,

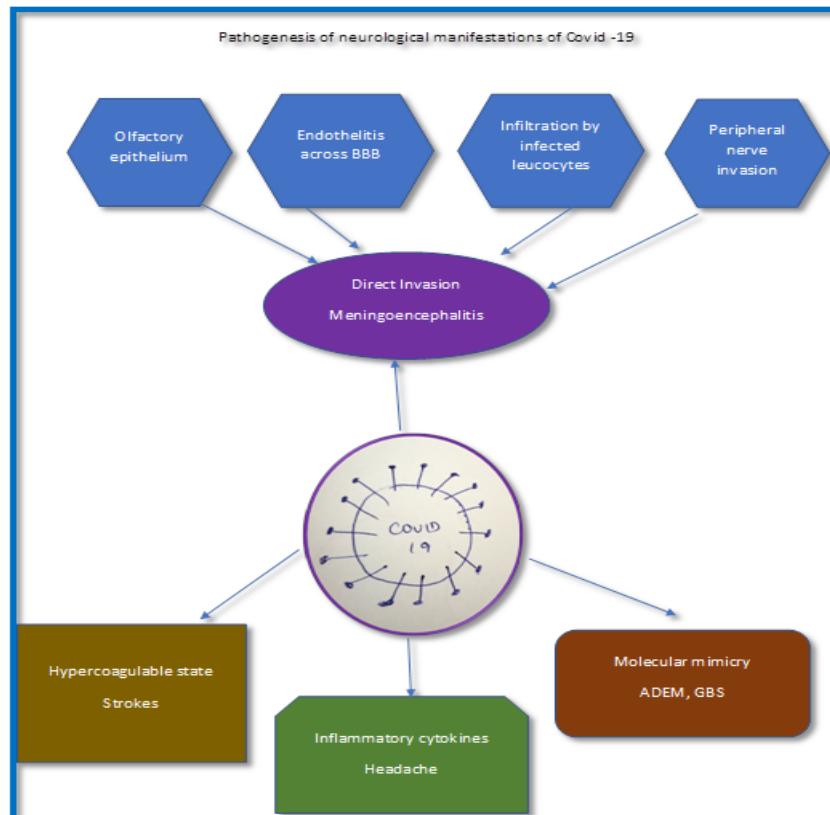


Figure 1: Pathogenetic mechanisms

approximately one in twenty patients had new onset headache, anosmia/hyposmia and altered sensorium as a direct manifestation of Covid-19 while approximately 9% had a new onset neurological disorder. (3) A recent meta analysis of 350 studies with 145,634 Covid 19 patients, one third had neurological manifestation. (4)

Pathophysiology

Covid -19 may cause neurological manifestations by multiple mechanisms- either by direct invasion of the CNS or by its effect mediated by increased cytokine release, hypercoagulable state or causing secondary autoimmune syndromes (Fig 1)

Invasion

Vulnerability

It is now known that SARS-CoV-2 has a spike protein on its surface that it uses to bind to the host cells. This it does via the angiotensin converting enzyme 2 receptors(ACE-2 R) present on the cells. The viral cellular tropism hence depends on the concentration of ACE-2 R in various cells in the body, thus explaining its predilection for airway epithelia. Similarly ACE-2 R is present on the olfactory epithelium and direct infection by Covid 19 causes olfactory loss even in the absence of rhinorrhea/nasal stuffiness.

ACE-R in brain : ACE-2 expression is seen in both the cytoplasm and surface membrane of various cells in the brain including neurons, oligodendrocytes and microglia.(3) The areas of brain which have concentrated expression of ACE-2 include substantia nigra, ventricles, middle temporal lobe gyrus, posterior cingulate cortex and olfactory bulbs. (3) Thus widespread expression of ACE-2 throughout the CNS makes it vulnerable to invasion by SARS-CoV-19 virus. (5)

Reaching the brain tissue

There are several postulations by which it is supposed that SARS-CoV2 reaches the brain.

It may enter via the olfactory nerve, infect the vascular endothelium, may be carried by the leucocytes across the blood brain barrier.

The other possible route which has been

demonstrated in other corona viruses may be by invasion of peripheral nerves initially and then the virus may travel retrograde towards the ganglion and via the synapses may spread to the CNS. (5)

Although there are few reports published suggesting the invasion of brain tissue, neurological manifestation such as encephalitis and seizures may also be caused by presence of inflammatory leucocytosis, elevated cytokines and metabolic derangement.

Stroke

The increased risk of cerebrovascular disease caused by Covid 19 is most likely multifactorial. There is a high level of inflammatory cytokines, pro-coagulants released during Covid -19 infection which then leads to a hypercoagulable state. Vascular endothelial cells infection causing damage to the endothelium with increase inflammatory vasculitis also contributes to an increased risk of both ischemic and haemorrhagic stroke. (5)

Post infectious manifestations.

Molecular mimicry mechanisms occur even in SARS-COV2 virus, similar to other viruses with epitopes which are similar to myelin component in the CNS and PNS. This causes an exacerbation of demyelinating disorders secondary to autoreactive T or B cells. (5). These result in both central and peripheral demyelinating disorders such as , acute disseminated encephalomyelitis(ADEM), transverse myelitis and acute inflammatory demyelinating polyneuropathy (AIDP). Other types of GBS can also occur due to interaction with other components of peripheral nerve.

Clinical manifestations

The studies suggest a wide range of neurological manifestations which are diverse. We can classify them into the following groups based on localisation of these symptoms. (fig 2)

1. Non specific symptoms including symptoms like headache, confusion, dizziness, fatigue
2. Psychiatric symptoms such as anxiety, depression and psychosis
3. CNS manifestations – cranial neuropathy-

anosmia, dysgeusias, encephalitis and encephalopathy, cerebrovascular accidents(CVA), ADEM , myelitis.

4. Peripheral nervous system manifestations such as -GBS
5. Musculoskeletal –e.g., myalgia

We can also classify the neurological manifestations based on the time of appearance – acute during Covid -19 infection- anosmia, dysgeusia, encephalitis, CVA, myalgias, post Covid 19 infection – GBS, ADEM and transverse myelitis and Delayed manifestations – long Covid syndrome

Non specific symptoms, anosmia and dysgeusia are the most frequently detected complaints. (4,6) Older age seems to impart a higher risk of developing neurological disease. (4)

Non specific symptoms

Headache

Headache is a common symptom seen in 12-57% of patients with covid-19 and can persist in 5-10% even after the remission of fever and other symptoms. (6-9) In a recent analysis of 2195 Covid 19 patients with headache, headache occurred most

frequently on the first day of the illness itself. (9) It was considered as the worst ever headache in around one third of patients. Most patients have a bifrontal or holocranial continuous oppressive headache of moderate intensity requiring medications. (9) A recent study suggested that presence of headache may be associated with a better outcome. (10)

Previous reviews also suggest similar findings. In most patients, headache fulfil the criteria for "Acute headache attributed to systemic viral infection" of ICHD -3 classification (i.e, headache is temporally associated with infection, severity mirrors the systemic infection severity and it is not attributable to other disorders); but the headache may mimic migraine headache or tension type headache in some. Treatment is symptomatic and naproxen or paracetamol can be given for relief.

Long Covid syndrome : Headache is one of the symptoms that can persist beyond 6 weeks even after the resolution of other symptoms or can start after a couple of months. These headaches commonly are similar to migraine headaches and respond to migraine therapy (eg., triptans as acute therapy and topiramate for long term therapy).

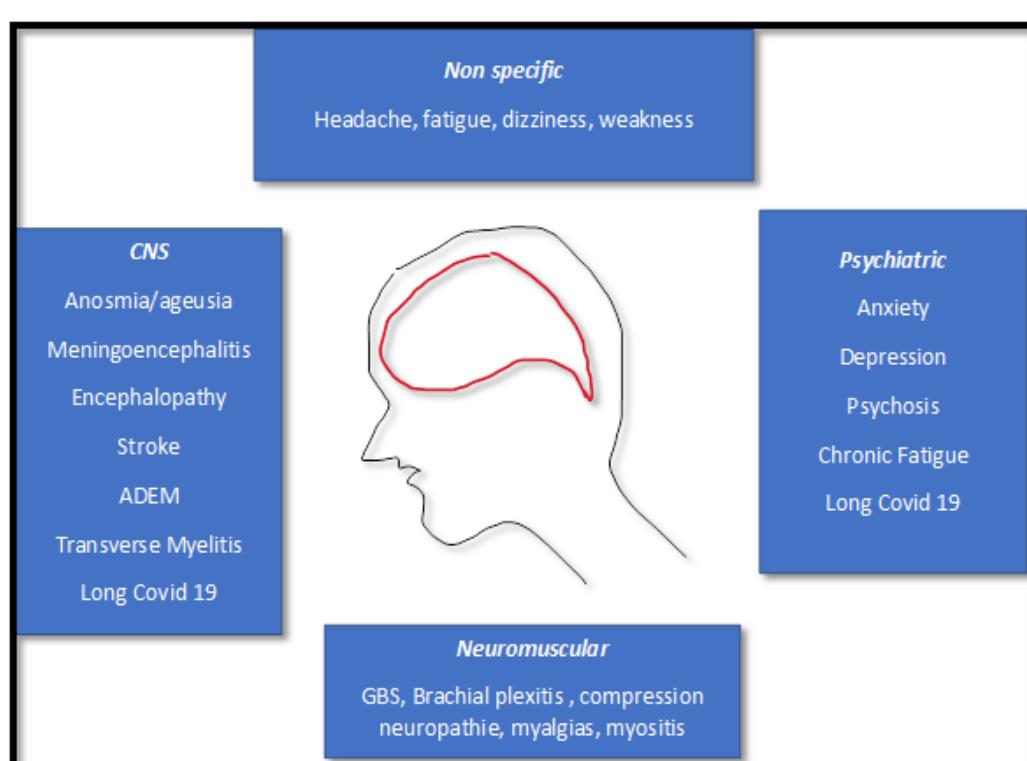


Figure 2 : Neurological manifestations of Covid 19

Sometimes headache may be associated with depression, anxiety and may be similar to chronic tension type headache. These may respond better to tricyclic antidepressants or anxiolytics. (11)

Other non specific symptoms

Other non specific symptoms occurred with varying frequency in different studies; generalised fatigue and weakness in roughly 35-40%, dizziness and sleep disorders in around 15-20%. (6) Fatigue can start in the second week of the illness and last for few weeks to even months. Although the exact mechanism is not known, SARS-CoV2 seems to target the hypothalamus paraventricular nucleus and the dysfunction is exacerbated by the other stressors associated with Covid-19. (12) There is no clear correlation between the disease severity and fatigue. (13) Some patients can develop a post Covid 19 chronic fatigue syndrome which can significantly impact the quality of life. Unfortunately there is no specific therapy for this aspect. Adequate rest, good food, slowly building up an active physical activity regime and giving enough time to recover only seems to be the way to treat. (14)

Psychiatric manifestations

Anxiety and depression can be seen in patients with Covid-19 and can persist for long time. Other psychiatric manifestations such as new onset psychosis, can be seen as a manifestation of the systemic toxic encephalopathy, drugs such as steroids and also due to the co-existing social stressful conditions. In a meta-analysis of studies

on Chinese patients, patients with covid-19 had all types of psychiatric manifestations which were moderate-to severe in intensity during the initial periods and reduced slowly over time. (fig 1) (15)

It is important to identify the presence of the psychiatric manifestations and take proper counselling and adequate therapy under the supervision of psychiatrist for the complete recovery of the patients.

CNS manifestations

The most common CNS manifestations include anosmia, ageusia which sometimes can be the only manifestations of Covid-19 patients. Racial factors may play a role with olfactory more commonly described in European and US population compared to Chinese population. Olfactory loss, in contrast to other viral infections can occur in the absence of rhinorrhea or nasal stuffiness, as it is due to the direct involvement of olfactory epithelium by SARS-CoV2 virus. Most series suggest that olfactory loss begins around 4-5 days after the onset of the other symptoms and lasts for a period of 8-9 days and the improvement commonly mirrors the general improvement of all systemic symptoms. Anosmia also seems to be a marker of less severe diseases in some studies. (16)

Bell's palsy – Case reports of patients presenting with facial weakness as an initial manifestation of Covid 19. The treatment should be of the underlying systemic infection with short course of steroids, eye care and facial nerve stimulation. (17)

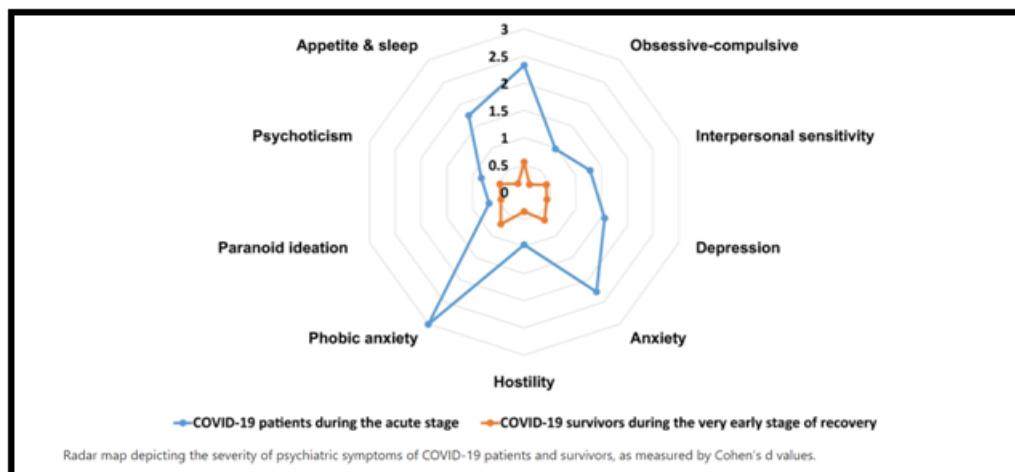


Figure 3: Xie Q et al -Severity of patients in acute illness and during early recovery (15)

Acute meningoencephalitis, encephalopathy, delirium, seizures

A life threatening complication, meningoencephalitis as a part of Covid 19 is more common among elderly compared to younger patients. (18) The clinical manifestations include confusion, drowsiness, cognitive impairment, seizures, rarely focal neurological signs. Symptoms may occur anytime from first day to the end of second week. There are no specific symptoms or imaging correlates to identify meningoencephalitis secondary to Covid-19. Brain imaging may be normal. Laboratory findings associated with meningoencephalitis, are raised CRP and D dimer levels. Cerebrospinal fluid analysis may show leucocytosis with elevated protein and Electroencephalogram(EEG) may show diffuse or focal slowing with focal epileptiform discharges. (19)

In patients with severe Covid 19, presence of hypoxia, other metabolic abnormalities and increased inflammatory cytokines might result in toxic/metabolic encephalopathy which has similar features. Usually, CSF abnormalities are not seen in these patients. In both the scenarios, patient may have delirium with either agitated or hypokinetic states.

Meningoencephalitis, encephalopathy and delirium all portend a poor prognosis. Unfortunately there are no specific medications for treating this complication and management is symptomatic. But it is preferable to do Brain imaging to look for infarcts or other abnormalities. EEG can help in identifying underlying seizures and to start antiepileptics if required. If the patient is very agitated, benzodiazepines may be given in low doses or atypical antipsychotics such as quetiapine may be prescribed. (20)

CVA

Strokes occur more commonly with Covid -19. Prevalence of COVID-19-associated stroke ranges from 0.9 to 46% [6]. The variability may be due to differences in the population being studied. Pooled data and meta analysis by Mishra S et al shows that 2% of Covid -19 patients develop stroke. (4) The direct evidence of possible increased risk comes

from comparative studies between influenza and Covid 19 induced strokes. Prevalence of COVID-19-associated strokes was 1.2% compared to only 0.2% in a retrospective cohort study of 1486 hospitalized influenza patients, even after adjustment for socio-economic factors [21].

Covid 19 induces a procoagulant state with injury to the endothelium causing a predisposition to develop ischemic strokes. Most common strokes have been due to large artery occlusions with infarcts with some secondary to lacunar infarcts.

Haemorrhagic strokes can also occur as the endothelium gets damaged with leaky blood brain barriers. The ratio of ischemic to haemorrhagic stroke is around 7:1. Strokes seem to be associated with increased age, more severe disease and other comorbidities. Studies have looked at the temporal association of stroke with Covid 19. A single study suggested that mild infection is associated with early onset and that severe infection have strokes which are later in course (2nd or 3rd week). (7) Among the laboratory parameters, elevated D-Dimer is a good predictor of ischemic events both cerebrovascular and cardiac. Elevated D dimer was associated with higher chances of thrombotic events (19.4% vs 10.2% with normal D dimer levels). [22] Thus it is important to actively start patients with elevated D-dimer levels (>1000 mg/dl) on anticoagulation to prevent risk of thromboembolism.

Management of stroke with Covid 19 – There is no difference in management of stroke among patients with and without Covid 19. Intravenous thrombolysis and mechanical thrombectomy can be performed in patients who come within the window period. But the disease process, chance of clot migration, presence of tandem lesions can make mechanical thrombectomy more difficult.

Haemorrhagic strokes are also managed in the same manner as is done with a non Covid 19 patient.

Another manifestation of procoagulant state can be a cerebral sinus venous thrombosis which can be identified by an MR venogram. These patients require heparin or low molecular weight heparin in a therapeutic dose and follow up with oral anti-coagulants for 6 months.

Neuroinflammatory syndromes- ADEM and transverse myelitis

Any viral infection can trigger an autoimmune process due to the process of molecular mimicry with the structures involved in the CNS and most of them can cause antibodies targeted towards myelin and oligodendrocytes. ADEM and transverse myelitis occurring one to four weeks after recovery from Covid 19 have been described in all ages. It can also occur before complete recovery. ADEM can manifest as drowsiness, obtundation or focal neurological deficits. It is important to identify this, especially in patients with severe Covid 19 on prolonged ventilation where patients may suddenly become drowsy or unresponsive. Diagnosis can be made with the help of MRI brain which usually show asymmetrical, bilateral and hyperintense lesions on T2-weighted/fluid-attenuated inversion recovery sequences. (23) Transverse myelitis classically present as paraplegia with bladder retention. These disorders respond well to pulse methylprednisolone given at the dose of 1gm daily x 5 days followed by a tapering dose of oral steroids over 10-15 days. In case there is no response, plasmapheresis can be given in these patients.

Covid 19 can also trigger some unusual neuroinflammatory syndromes. One of them is opsoclonus myoclonus ataxia syndrome which is increasingly seen after Covid 19. It is characterised by the varying combinations of cerebellar ataxia, abnormal ocular movements and myoclonus. (24) It may respond to intravenous pulse methyl prednisolone and if required intravenous immunoglobulins may need to be given. Others include brain stem encephalitis and acute hemorrhagic ADEM. There seems to be no correlation between the severity of the disease and occurrence of these syndromes.

Peripheral nervous system manifestations

Theoretically neuroinvasion is possible with the virus directly involving the peripheral nerve, however there has been no reports of neuritis caused directly by the virus. Immune mediated neuropathies such as GBS and brachial plexitis are the most common peripheral nervous system presentations. Based on the principle of molecular mimicry, various types of GBS – acute idiopathic demyelinating neuropathy, acute motor axonal neuropathy, acute motor

sensory axonal neuropathy, Miller Fisher variants have all been described after Covid 19. Most present with ascending flaccid areflexic quadripareisis with lower cranial nerve involvement and rarely bulbar involvement. Miller Fisher variant in its pure form presents as a sensory ataxic syndrome with ophthalmoparesis. The diagnosis can be confirmed by doing an electrophysiological test which can also help in categorising the GBS. The clinical syndrome is similar to non covid patients. Treatment is based on the severity of the disease. Ambulatory patients are managed conservatively with monitoring. Patients who cant walk 5m without support are treated with intravenous immunoglobulins or plasmapheresis. Steroids are not of much use except as an adjunctive treatment in those who have autonomic disturbances. (25)

Brachial plexitis presents as a painful weakness with sensory loss over one arm. Treatment is with intravenous methylprednisolone over 5 years followed by oral steroids.

In severe patients who have received prone ventilatory support, compression neuropathies involving median, ulnar nerves, brachial plexus can also occur. Critical illness neuropathy has also been identified in some patients. Treatment modalities are same as those seen in non covid illnesses. (25)

Neuropathic pain can occur as a complication of any of the peripheral neuropathies and can be treated with gabapentin, pregabalin, tricyclic antidepressants.

Musculoskeletal

Myositis, myalgias and NMJ disorders have also been described though they are rare compared to the other complications. Patients can present with myalgias and elevated creatinine phosphokinase with proximal muscle weakness. Inflammatory myositis with necrotising autoimmune myopathy also have been described. Intravenous pulse methylprednisolone followed by oral steroids are the main stay of treatment in these patients. (25)

Unusual complications of treatment and Covid -19

Rhinocerebral mucormycosis

Invasive rhinofaciocerebral muormycosis caused by Rhizopus species has increased in prevalence due

to the involvement of covid-19 patients by the fungus. This was characteristically observed during the second wave in India. Mucormycosis was an uncommon disease seen rarely in patients with uncontrolled diabetes before the sudden surge in the disease.

These patients typically present with facial pain along with a black eschar formation over the hard palate, sinus tenderness followed by orbital involvement resulting in swelling, redness and pain in the eye with restriction of eyeball movements. Once the fungus spreads to the cavernous sinus, it spreads rapidly to the opposite side. The fungus can invade the bone and can involve the brain rapidly causing seizures and focal neurological deficits.

The current association with Covid -19 seems to be multifactorial.

Covid 19 involves the olfactory epithelium which probably creates a breach. It also causes an reduction in immunity by lymphopenia, reduction in CD8 cells along with endothelial damage and thrombosis, restricting immune responses to fungal infections.

Addition of steroids as therapy can possibly tilt the balance in sugar control especially in diabetics, possibly leading to diabetic ketoacidosis which can predispose them to developing mucormycosis. Associated acidosis and increased iron in this setting can lead to an increased risk of mucormycosis. (26)

Unfortunately treatment involves extensive debridement of tissues invaded by fungus leading to enucleation in most patients along with long term therapy with amphotericin B or posaconazole or isavuconazole.

It is important to monitor and keep blood sugars in control when administering steroids for the various manifestations of Covid 19 to keep this dreaded complication at bay.

Long Covid 19 syndrome

These are symptoms of covid -19 which are persistent even after 12 weeks of disease. Most of the symptoms are the continuing effects of the damage caused by the infection with impact on respiratory, cardiac, cutaneous, and nervous system predominantly. These symptoms may be persisting

from the acute phase, may be a flare up of neuropsychiatric symptoms or new symptoms may arise. Patients with long Covid-19 syndrome have poorer quality of life.

Neurological symptoms are more common among hospitalised patients, especially those who had been critically ill. These include headache, myalgia, weakness, vertigo, persistent anosmia/ dysgeusia to serious complications of stroke, seizures and encephalopathy. (27) Brain fog is a term given to a group of cognitive dysfunctions such as memory impairment, inability to concentrate, confusion and dullness. This is a common feature of Long-COVID-19 syndrome. These effects may be due to dysfunctional pericytes causing vascular impairment and hypoxia and mitochondrial dysfunction causing mitochondrial dysfunction. (27) Apart from this, patients may have psychiatric manifestations of increased anxiety, impaired sleep and depression causing significant impairment in quality of life. Long Covid 19 syndrome is commoner in elderly, those with severe disease in acute phase, underlying comorbidities, hyper inflammatory state and is more common in women.

These patients need to be followed up closely and it is important to look out for these symptoms. The Long-COVID-19 subjects need close follow-up for monitoring early, intermediate, and late complications. (27)

Neurological and psychiatric manifestations can be devastating to patients and their families and need to be addressed by referral to psychiatrists and psychologists for pharmacotherapy and counselling. Deficiencies in Vit D can be easily corrected and can help in improving the condition overall.

Covid 19 in patients with pre-existing neurological disorders

The course of Covid 19 is varied in patients with pre-existing neurological disorders. The pandemic made it difficult for these patients to receive adequate care even when they were not affected. Course of disease was similar to healthy controls in patients with movement disorders (Parkinson's disease), multiple sclerosis and headache. Patients with prior strokes had higher rates of requiring admission into intensive care units. Patients with

neuromuscular disorders were more likely to become hypoxic easily and required ventilatory support. Similarly patients with sleep disorders had higher prevalence of sleep apneas and intubations. Patients with dementia had a higher mortality rates. (28) Though the Covid 19 infection infects the olfactory epithelium and may spread to the brain, theoretically leading to Parkinson's disease, there are no reports suggesting that PD can be caused by Covid 19.

Conclusions

Neuropsychiatric complications of Covid are multiple and can involve any part of the neuraxis. The effects may be initial or can last months after the infection. Treatment is only possible for a few of these disorders and preventing the disease itself by vaccination is the best management policy.

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COVID-19 and Mucormycosis

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INTRODUCTION

Mucormycetes is ubiquitous fungi found throughout nature. It generally favours tropical conditions, which partly explains its higher incidence in tropical settings (1). It has been estimated that the incidence in the Indian subcontinent is more than 100 times when compared to the incidence in Canada (2). The spores of these fungi are easily aerosolized and are readily dispersed in the environment. These spores are airborne and can invade a susceptible host. During the second wave of Coronavirus disease 2019 (COVID-19), a massive spurt of mucormycosis was seen in post-COVID cases in the Indian subcontinent (1). Of the several genera of mucormycetes that can cause human infection, the most common ones in the pre-COVID era in India include Rhizopus, Apophysomyces, Lichtheimia and Rhizomucor species (2). Similar species distribution was seen in the post-COVID cases as well. The chapter discusses the risk factors, clinical features, diagnosis and management of these cases.

Risk factors for COVID-associated-mucormycosis (CAM):

Two main risk factors for CAM are discussed here.

- Diabetes mellitus (DM): Studies have shown that SARS-CoV-2 ACE-2 receptors are present in pancreatic islet cells as well. This may partly explain higher dysglycemia in COVID patients. Also, DM is a risk factor for both severe COVID and mucormycosis (3). India has the second-largest number of adults with DM (4). DM has been identified as a risk factor in more than half to two-thirds of all mucormycosis in Indian studies. A good proportion of these patients have Diabetic ketoacidosis (DKA) as well (4). In the COSMIC study that included

2826 patients with ROCM, DM was present in 78% of all patients (5). In fact, the diagnosis of mucormycosis has unmasked DM in many patients (4). Hyperglycaemic and acidic pH render the phagocytic cells dysfunctional, thereby making a patient prone to fungal invasion. The acidic pH of serum impairs the chelating ability of transferrin as well, and therefore haemoglobin-free iron becomes readily available for the fungus to use. Elevated glucose and iron levels lead to increased cell surface expression of GRP-78, which is a receptor for the mucormycetes. Higher serum levels of GRP78 have been seen in COVID-19 compared to healthy controls and non-COVID-19 pneumonia.

- Steroid use: Steroid use has been identified to be an important risk factor for mucormycosis (6). Besides causing hyperglycemia which is an identified risk factor for mucormycosis, it causes impairment of innate immune function. The indiscriminate use of steroids in COVID patients could have been an important cause of CAM (3). In a study by Patel et al. (EID 2019), 35% and 67% of the steroid prescriptions in early and late CAM, respectively were inappropriate (7). In the COSMIC study, 87% of the patients with CAM were treated with corticosteroids (21% for > 10 days) (5). Dysregulated immune response may be seen in COVID patients irrespective of steroid use as well. COVID patients have been shown to have lymphopenia which results in an absolute decrease in CD8+ and CD4+ T-cells, which are essential mediators for immune function.

Clinical features

Most patients develop symptoms of mucormycosis after 2-4 weeks of the onset of COVID symptoms. In the COSMIC study, 56% developed mucormycosis 14 days after COVID-19 diagnosis. In the study by Patel et al., the median day of onset of post-COVID mucormycosis was 18 days. The clinical features depend on the site of involvement. The two most common types of CAM are discussed here.

- a. **Rhino-orbital-** This is the most common type of CAM (3). The infection begins from the sinus and can rapidly spread to involve orbits and the brain. It can also progress towards the palate (causing perforation) and mandible. Blackish discolouration due to necrosis of the involved sites can be seen in the later stages of the disease. This is the reason the disease has been colloquially said to be caused by a 'Black fungus'. It must, however, be noted that the culture of fungus is not black in colour.
- b. **Pulmonary-** This site is comparatively less common in CAM (3). It is also easier to miss as it can be assumed to be a manifestation of long COVID. The patients present with cough, expectoration with blackish discolouration, and haemoptysis.

Diagnosis

a. Clinical suspicion

It is important to suspect mucormycosis if the patient has typical risk factors and suggestive clinical features. Laboratory confirmation may be time-consuming, and therefore empiric initiation of therapy is warranted in those with high clinical suspicion.

b. Radiology

- Areas of increased density and homogeneous opacification of the sinus cavity can be seen on computed tomography (CT) scans in ROCM cases. CT is also sensitive for noting bony erosions. In patients with pulmonary mucormycosis, multiple nodules (>10 nodules are suggestive), cavitation, reverse halo sign and pleural effusion can be seen (8).

- Magnetic resonance imaging (MRI) is more sensitive for the diagnosis of ROCM as invasion/involvement of soft tissue and vessels can be appreciated (9). Infiltration of the periantral fat plane is the earliest imaging finding in patients with ROCM. Thickening and lateral displacement of the medial rectus muscle can also be seen. The lesions are usually hypointense on T2 and hypointense on T1 weighted images.

c. Microbiological diagnosis

- Following specimens can be used for diagnosis: nasal discharge, sputum, biopsy material, tissue material and aspirate. Swabs are not an acceptable sample. It must be noted that the tissue should not be ground while processing as it affects the culture yield (10).
- Direct microscopy (using KOH) is one of the fastest ways to make a reliable diagnosis of mucormycosis. KOH wet mounts show broad, aseptate, ribbon-like hyphae with a right-angle branching at irregular intervals (8). The addition of calcofluor makes the KOH mount more sensitive
- Histopathology shows angioinvasion, necrosis and infarcts in addition to fungal hyphae. GMS stain is helpful for fungal hyphae detection (8).
- Culture may be negative in many patients, and it is not essential to make a diagnosis of mucormycosis (8). The fungus grows in 2-3 days on Sabouraud dextrose agar in those where the culture is positive.

(Figures - see Color pages Section)

Management

a. Control of underlying disease

Control of the underlying disease is paramount to halt the disease progression. Unnecessary steroid prescriptions should be avoided. Intensive control of hyperglycemia in diabetic patients is crucial.

b. Surgical debridement

Aggressive debridement of involved tissues

is the most critical part of the management plan (9). Since tissue necrosis leads to poor penetration of antifungal agents, debridement of necrotic tissues is essential for the antifungals to be effective. Surgery has been shown to be an independent variable for favourable outcomes. Early surgery is important before the disease has progressed to the central nervous system.

c. Specific antifungal therapy

Delay in antifungals increases mortality. Therefore, urgent administration of antifungals in those with high suspicion of the disease is the standard of care.

i) Amphotericin B: Amphotericin B is the drug of choice for the management of mucormycosis. The liposomal form is recommended because of its favourable toxicity profile. Liposomal amphotericin B is used at 5-10mg per kg per day (9). In those with CNS involvement, 10 mg/kg is recommended (9). However, liposomal forms are costly, and in resource-limited settings, deoxycholate amphotericin has been used in its place despite the limited data (10). A dose of 1-1.5 mg/kg is recommended. Deoxycholate Amphotericin B is cheap but associated with renal toxicity and hypokalemia. However, it must be noted that acute kidney injury due to amphotericin B is reversible and can be prevented to some extent with adequate hydration.

ii) Posaconazole: The data for using posaconazole as an alternative to amphotericin B is limited (10). Oral posaconazole can be used, however, for step down therapy. Oral posaconazole is available as suspension (200 mg QID) or tablets (300 mg BD on Day 1 followed by 300 mg OD on Day 2). The bioavailability of oral posaconazole (especially suspension form) is highly variable and influenced by food. To improve absorption, it is administered with fatty food or acidic beverages. Therapeutic drug monitoring (TDM), although desirable, is available in only a few centres in the country. It does not have good CNS penetration and,

therefore, may not be very useful in those with CNS extension.

iii) Isavuconazole: Similar to posaconazole, the data for using posaconazole as an alternative to amphotericin B is limited. Oral tablets (200 mg TDS for two days followed by 200 mg OD) can be used for step-down therapy. TDM may not be required for isavuconazole, and it has good penetration as well.

iv) Iron chelation therapy: As free iron is important for the pathogenesis of mucormycosis, it has been suggested that chelators like oral deferasirox can have fungicidal activity. However, the data is limited for its recommendation for routine management.

v) Adjuvant strategies: Some strategies have been proposed based on small series. However, none of them are routinely recommended. Hyperbaric oxygen can be used as the high pressure of oxygen improves neutrophil count and oxidative killing by antifungals. Local irrigation with amphotericin during surgery has been tried in some reports.

The duration of antifungals is uncertain. No randomized trials have evaluated the type, dose and duration of antifungals (10). A prudent approach is to treat initially with 3-6 weeks of amphotericin B followed by a step-down therapy with posaconazole or isavuconazole. The duration of antifungals depends on the clinical and radiological resolution. Most experts treat it for six months or more.

CONCLUSION

Mucormycosis is a potentially fatal condition precipitated by poor sugar control and steroid use in patients with COVID-19. Early identification and aggressive management are the key to improving outcomes.

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Nephrology and COVID-19



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The first outbreak of a cluster of pneumonia cases linked to a novel corona virus in Wuhan, Hubei, China occurred in November 2019. The virus, identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a predominantly respiratory disease with multisystem involvement designated as COVID-19 by the World Health Organization. In March 2020, the WHO declared COVID-19 as a global pandemic. Globally, as of 14 September 2021, there have been 225,024,781 confirmed cases of COVID-19, including 4,636,153 deaths.

In India, from 3 January 2020 to 14 September 2021, there have been 33,289,579 confirmed cases of COVID-19 with 443,213 deaths, which is widely considered to be an underestimate.

Kidney Involvement in Covid-19

Although Covid-19 is predominantly a lung disease, it can also affect the kidney in a multitude of ways. The most common renal manifestation is Acute Kidney Injury (AKI), which increases the risk of prolonged hospital stay, worse outcomes and mortality¹. The presence of Chronic Kidney Disease (CKD) is an important comorbidity that increase the risk for morbidity and death in Covid-19².

The management of patients with renal failure is beset with challenges, particularly in a resource poor setting, where allocation of dialysis machines and staff and ensuring safety of healthcare personnel is an issue. There are also important technical issues with the provision of safe and effective renal

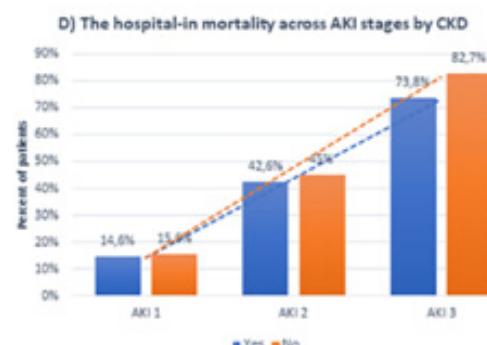
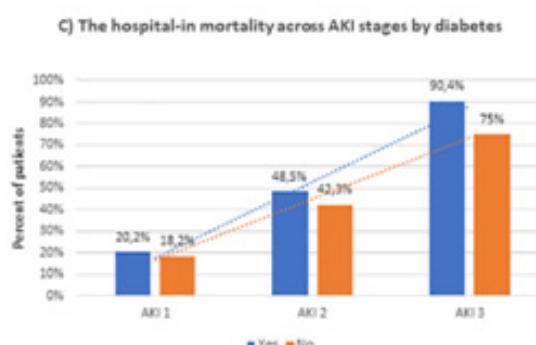
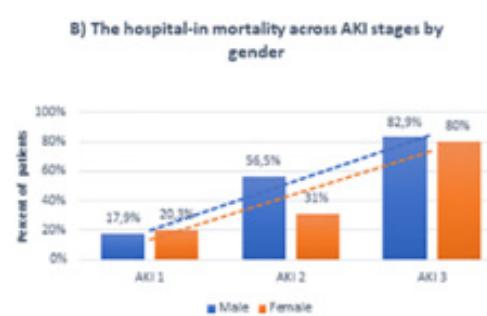


Figure 1 The in-hospital mortality rate³ across acute kidney injury (AKI) stages by age (A), gender (B), diabetes mellitus (C), and chronic kidney disease (CKD) (D).

replacement therapy or dialysis in Covid-19.

Definition of Acute Kidney Injury (AKI)

AKI is defined by Kidney Disease: Improving Global Outcomes (KDIGO) as an abrupt (within hours) decrease in kidney function, manifested as an increase in serum creatinine and decrease in urine output.

Epidemiology of Acute Kidney Injury

According to one metanalysis⁵, the prevalence of AKI among a population of mostly hospitalised Covid-19 patients was around 17%, and 5 % required some form of renal replacement therapy. Around 77 % of patients with AKI had severe Covid-19, and approximately 52% died.

AKI parallels disease severity. Around one-third of patients requiring intensive care have AKI, as do three-quarters of all intubated patients⁶.

In India, the data on AKI in Covid-19 is evolving, with wide heterogeneity in testing and sampling being an epidemiological challenge.

According to one retrospective study⁷ from South India, the incidence of AKI among 718 adult COVID-19 cases was 7%. Notably, this study excluded patients with CKD at baseline and those with a renal transplant.

Clinical features of AKI

Decreased urine output and elevated serum creatinine define AKI. Proteinuria and haematuria, manifested as abnormalities in urinalysis, are common in Covid-19 related AKI. In one study⁸ of 3993 hospitalized patients with Covid-19, 1835 (46%) patients had AKI. In 435 patients with AKI,

84% had proteinuria, 81% had microscopic hematuria, and 60% had leukocyturia. These abnormalities reflect kidney injury and are detected by urinary dipstick. They can occur in the absence of or predate significant rise in serum creatinine.

The protein found in urine is predominantly lower-molecular weight proteins of non-albumin type, reflecting tubular rather than glomerular origin. Indeed, proximal tubular injury that manifests as Fanconi syndrome can occur in the setting of AKI.

Table 1 Clinical Features of AKI

Common

- Decreased urine output
- Elevated serum creatinine and BUN
- Proteinuria < 2gm
- Microscopic hematuria
- Leucocyturia

Rare

- COVID-19-associated nephropathy (COVAN)
- Fanconi syndrome

Rarely, AKI can be secondary to glomerular disease, called COVID-19-associated nephropathy (COVAN⁹), and is associated with significant albuminuric proteinuria and collapsing glomerulopathy on renal biopsy.

Other glomerular diseases associated with Covid include:

- antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
- anti-glomerular basement membrane antibody disease
- IgA nephropathy

AKI Stage	Serum Creatinine Increase	Urine Output
1	1.5–1.9 times baseline OR $\geq 26.5 \mu\text{mol/L}$ (0.3 mg/dl) increase within 48 hours	<0.5 ml/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/hour for ≥ 12 hours
3	3.0 times baseline OR increase in serum creatinine to $\geq 353.6 \mu\text{mol/L}$ (4.0 mg/dl) OR start renal replacement therapy	<0.3 ml/kg/hour for ≥ 24 hours OR anuria for ≥ 12 hours

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Figure 2 Definition of AKI⁴

Although proteinuria and hematuria occur early in disease, elevation in serum creatinine and the need for RRT tends to occur later in the course of the disease compared with non-Covid AKI.

Pathophysiology of Acute Kidney Injury in Covid-19

Risk Factors for AKI in Covid-19.

There are several causes and risk factors for AKI in Covid-19. (Table 2)

1. Age: Elderly patients have a natural decline in GFR with age and poor functional renal reserve. This makes them more vulnerable to AKI.
2. Comorbid conditions: the presence of diabetes, hypertension, heart failure, chronic liver disease compromises renal vasculature and hemodynamics and increases the risk of AKI.
3. Chronic Kidney Disease results in fewer functioning nephrons and such a kidney is more vulnerable to additional insults and AKI.
4. Obesity
5. Renal hypoperfusion secondary to shock, fever, vomiting and diarrhea.
6. Nephrotoxicity of NSAIDS, antibiotics, antivirals, and contrast media.

Table 2 : Potential Risk Factors for COVID-19 AKI¹

Demographic Risk Factors	Risk factors for AKI at admission	Risk factors for AKI during hospitalization
Diabetes Mellitus	Respiratory status	Nephrotoxins (medications, contrast exposure)
Hypertension	Degree of viraemia	Vasopressors
Cardiovascular Disease	Non-respiratory organ involvement, e.g. diarrhoea	Ventilation, high positive end-expiratory pressure
Heart Failure	Leukocytosis	Fluid dynamics (fluid overload or hypovolaemia)
Immunosuppressed state	Lymphopaenia	
Chronic kidney disease	Elevated markers of inflammation, e.g. ferritin, C-reactive protein, D-dimers	
Smoking History	Hypovolaemia/Dehydration	
Genetic risk factors (e.g. APOL1 genotype; ACE2 polymorphisms)	Rhabdomyolysis	
Obesity	Medication exposure, e.g. angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs), statins, nonsteroidal anti-inflammatory drugs (NSAIDs)	

7. Rhabdomyolysis
8. Direct cytopathic effect of virus on tubular cells.
9. Mechanical ventilation
10. Hypercoagulable state leading to diffuse vascular thrombosis
11. Cytokine storm
12. Renal compartment syndrome

In a typical patient, more than one factor is often involved, and a confluence of risk factors often leads to more severe AKI.

Pathophysiology of AKI¹¹

AKI in Covid-19 is intimately linked to inflammation, hypercoagulable state, endothelial damage, and the renin angiotensin system.

SARS-CoV2 can directly infect the kidney and virus can be found in urine. Our understanding of the role of viral tropism in AKI is evolving. Whether direct viral infection of the kidney causes AKI remains unproven¹².

The Role of Inflammation

Tissue damage resulting from hyperinflammation, and dysregulated immunity can lead to AKI. The term "cytokine storm" is much in the news and has become almost synonymous with Covid-19. In

reality, it is a misnomer. There are many viral and bacterial diseases with a more severe rise in inflammatory markers than Covid-19. And yet, the term is instructive.

Dysregulated immunity in Covid-19 encompasses lymphopenia, increased complement activation, suppression of interferon activity, and elevated cytokines.

Endothelial Damage

High d-dimer levels and microvascular thromboses are the signature of endothelial dysfunction in Covid-19 and are a harbinger of severe disease and AKI. Impaired endothelium due to pre-existing comorbidities such as diabetes, hypertension, cardiovascular disease and hyperlipidemia is a setting for severe Covid-19.

Diffuse Activation of Coagulation Cascade

Many viral infections can cause increased coagulation, but Covid-19 is unique in the extent to which this happens. Both microvascular and macrovascular thromboses are common and can lead to organ dysfunction. The release of damage associated molecular patterns (DAMPs), endothelial activation, activation of platelets, and triggering of the complement cascade can lead to an increased thrombotic tendency. Microthromboses within the kidney can lead to thrombotic microangiopathy.

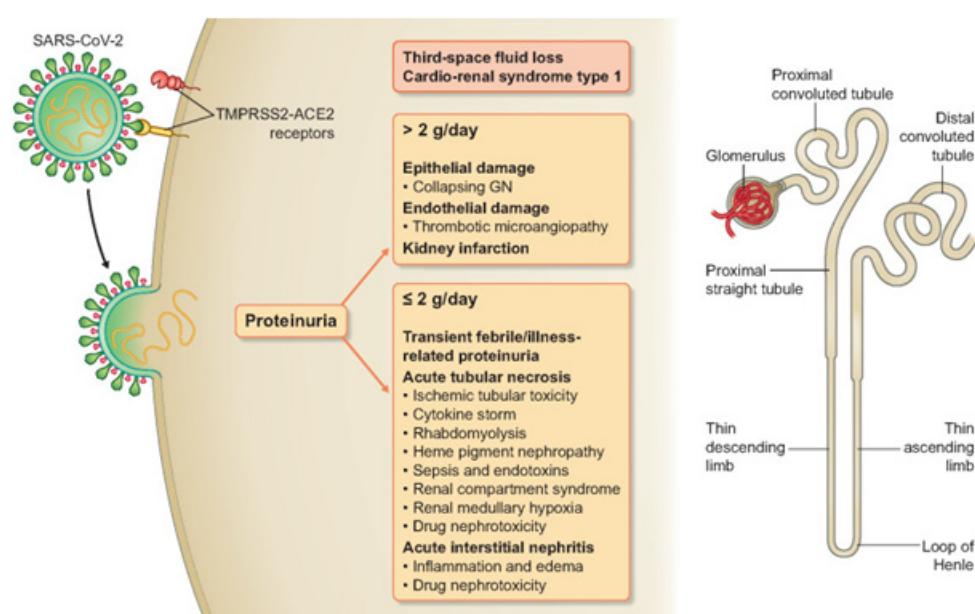


Figure 3 Pathophysiology of AKI¹³

The Renin Angiotensin System

Interaction between SARS-CoV-2 and Angiotensin II receptors is a potential mechanism contributing to infectivity of the virus and AKI. Initially, there was speculation that ACE inhibitors might potentiate the severity of disease, but multiple studies have now shown that there ACEIs and ARBs are safe to use and stopping them in a Covid-19 patient might lead to harm.

Renal Histology in Covid-19

(Fig 4. see Color pages section)

Renal biopsy is rarely performed in Covid-19 and is usually not necessary. Many of the patients are on anticoagulation and are critically ill, so it is a challenging procedure to perform in those who need it most.

In most cases the diagnosis is obvious in the setting of critical illness and hypotension and other risk factors for acute tubular necrosis. However, a biopsy is necessary when the clinical picture suggests a diagnosis other than ATN:

- >1 gm of proteinuria,
- active urine sediment
- RBC casts in urine
- Multiple potential causes for AKI (NSAIDs, antibiotics, toxins, etc)

In patients in whom multiple diagnoses are a possibility – e.g., a kidney transplant recipient with rising creatinine and Covid-19, in whom rejection of the transplant kidney is an important differential, a biopsy becomes mandatory.

Worldwide, the renal biopsy findings in cases series of Covid-19 are as follows:

- Acute tubular necrosis (most common)
- Acute interstitial nephritis
- Collapsing focal segmental glomerular sclerosis (COVAN)(very rare)
- Cortical necrosis

Sometimes the renal biopsy can highlight the toxic effect of therapy. Covid-19 saw the rampant use of high doses of Vitamin C, administered orally as well

as intravenously. Renal biopsy findings in such patients have shown the effects of oxalate toxicity.

Evaluation of AKI

Acute Kidney Injury in Covid-19 should be evaluated on the lines of AKI from any other cause, with the added caveat that unnecessary contact with the patient should be minimised.

The following investigations may be considered depending on the clinical scenario:

Urinalysis

- o Should be performed in all cases.
- o Urinalysis can be performed by automated methods or by dipstick. Examination of the sediment to detect casts should be done manually and is quite safe as urine is not considered very infectious.

Blood urea nitrogen and serum creatinine

- o An elevation in serum creatinine by 0.3 mg / dl is diagnostic of AKI.
- o The ratio of BUN/S.Creatinine can help differentiate between pre-renal AKI, which responds to fluid therapy, and intrinsic AKI (mostly ATN), which needs judicious fluid management and attention to multiple factors.

Serum sodium, potassium, and chloride

- o Hyperkalemia can occur in renal failure, and severe hyperkalemia not responsive to medical treatment is an indication for dialysis.
- o Disorders of sodium reflect water balance.
- o Chloride shifts can occur in response to acid-base disorders

Abdominal ultrasound

- o As the first step in the evaluation of AKI, it's important to rule out urinary tract obstruction, and an ultrasound will do that quickly and non-invasively.
- o It can give clues about the presence of CKD
- o It can suggest alternative diagnoses for AKI- kidney stones, pyelonephritis, renal arterial or venous thromboses (using Doppler

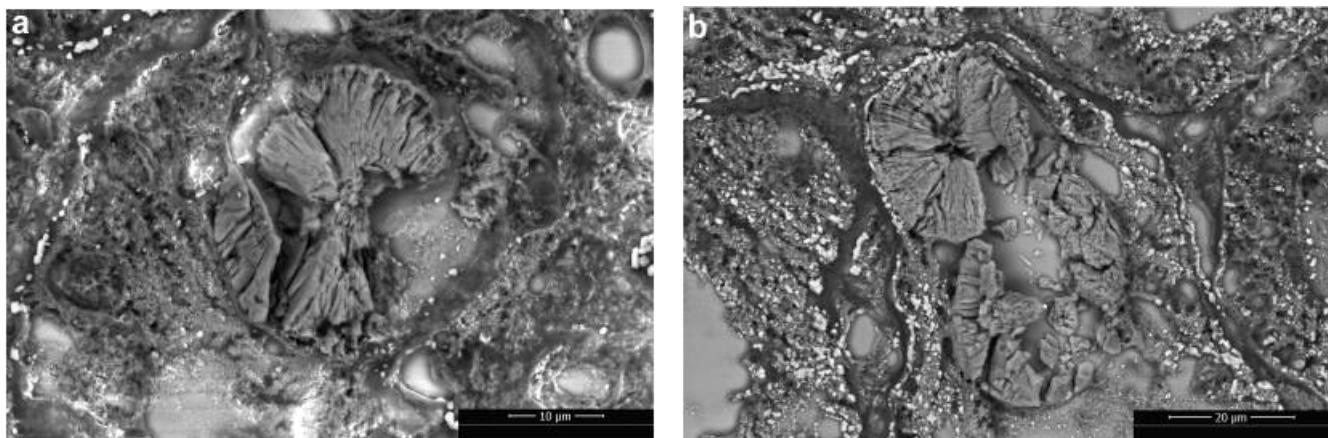


Figure 5 : Scanning electron microscope photographs¹⁵ of calcium oxalate monohydrate crystals in the tubular lumen . Crystals show the typical rose-cut-shaped appearance.

probe)

Urine protein-creatinine ratio

- o Helps to quantify proteinuria.
- o A ratio less than 2 is usual in ATN or interstitial nephritis.
- o A ratio greater than 3.5 (nephrotic range) suggests a diagnosis of COVAN or other glomerular pathology.

Creatine phosphokinase

- o This is elevated in rhabdomyolysis, which is a cause of AKI in Covid-19.

Arterial Blood Gases

- o Helps to diagnose acid-base disorders and measures blood levels of oxygen and carbon dioxide.

Renal Biopsy

- o Gold standard for the diagnosis of many renal diseases but is rarely necessary in Covid-19.
- o Becomes necessary when significant proteinuria is present, or when a diagnosis other than ATN is being considered.
- o Technically challenging to perform in an anticoagulated patient, particularly when the operator is garbed in a full PPE kit and a respirator mask.

Management of AKI

Acute Kidney Injury in Covid-19 falls broadly into two categories and parallels the overall severity of

the disease:

- Non-Dialysis
- Dialysis-requiring.

Management of Non-Dialysis AKI

This degree of AKI is mild and responds to conservative management. It probably reflects a pre-renal state, with the possible additional effect of nephrotoxic medications.

Treatment depends on addressing the underlying cause and involves optimisation of fluid status with the judicious use of oral and iv fluids. Balanced crystalloids such as Ringer's Lactate or Plasmalyte-A should be preferred as large volumes of normal saline can cause hyperchloremic metabolic acidosis.

It is possible to exacerbate lung pathology, oxygenation and cause fluid overload and breathlessness due to excessive and overenthusiastic administration of intravenous fluids. As much as possible, one should make use of objective criteria such as dimensions and collapsibility of inferior vena cava to avoid excessive administration of fluids.

Obviously, a through survey should be made of all nephrotoxic medication use in the present and recent past, and such drugs should be eliminated.

Although mild AKI is easily treated, it raises the risk of mortality in Covid-19.

Management of Severe AKI

AKI that requires dialysis often occurs in the setting of severe Covid-19. The need for dialysis can also be precipitated by AKI superimposed on pre-existing

renal dysfunction (CKD).

Renal dysfunction of a severity that necessitates renal replacement therapy (RRT) or dialysis is a significant predictor of mortality¹⁶.

The purpose of dialysis is to replace kidney function temporarily and safely. There is no evidence that dialysis improves kidney function, and there is plenty of data to suggest that it may delay renal recovery.

The absolute indications for doing dialysis in Covid-19¹⁷ are not very different from other settings and are as follows:

- Volume overload that is refractory to diuretics
- Hyperkalemia that is life threatening or not responding to conservative measures
- Severe metabolic acidosis that is unresponsive to treatment of underlying cause and other conservative measures including bicarbonate administration.
- Encephalopathy attributable to uremia
- Platelet dysfunction and bleeding that is due to uremia.

In addition to the above absolute indications, there are several relative indications, including an anticipated need for dialysis over the next few hours, to provide parenteral nutrition support, and to aid in the management of heart failure.

Once the need for dialysis has been established, it is important to choose the modality of dialysis (hemodialysis or peritoneal dialysis), and if hemodialysis is preferred whether to choose an intermittent or a continuous modality.

Wherever possible, it is better to co-localise patients who need dialysis within the same ICU, to enable fewer number of dialysis staff to manage more patients and thereby limit exposure to personnel. There is no need to make special provision for discarding dialysate effluent.

Extra-long tubing can be used to locate the dialysis machine outside an isolated ICU room, so that staff can safely operate the machine without being exposed to the virus.

In general, patients who are critically ill and are having hypotension or requiring pressors are more suited for Continuous Renal Replacement Therapy¹⁹ (CRRT). This allows the provision of continuous dialysis for up to a few days, with fluid removal that can be tailored as per metabolic requirements and allows adjusting for intake on an hourly basis. CRRT is particularly suitable for those who have heart failure or cirrhosis of liver, and for patients who are hypercatabolic – who form a large segment of the ICU population in a Covid-19 setting.

The disadvantage of CRRT is that it is an expensive modality and requires dedicated dialysis staff. The filter is prone to clot, more so in Covid-19 given the attendant hypercoagulable state, and it needs some form of anticoagulation. The usual anticoagulants are heparin or regional citrate. In those in whom anticoagulation is absolutely contraindicated, the circuit can be managed by a diligent and vigilant dialysis technician by administering regular saline flushes to keep the filter free of clots, but this is a cumbersome process.

In patients who require continuous therapy but cannot afford it or when the CRRT machine is not available, prolonged intermittent renal replacement therapy (PIRRT) or sustained low-efficiency dialysis (SLED) can be performed with a hemodialysis machine.

Alternatively, a CRRT machine can be used to deliver a higher dose of dialysis for 12 hours at a time, thereby allowing more patients to be treated with the same machine.

In patients who are hemodynamically stable, intermittent hemodialysis can be performed safely.

Peritoneal Dialysis²⁰ is an option when hemodialysis resources are under strain. The procedure involves insertion of a soft peritoneal dialysis catheter into the abdomen and using the peritoneum as a dialysis membrane. This can be done bedside. Sterile peritoneal dialysis fluid is instilled into the abdomen, allowed to dwell for a few hours, and then the effluent is let out and discarded. This process can remove uremic solutes. But it may not be an adequate modality in hypercatabolic patients whose

	Advantages	Disadvantages
CRRT	<ul style="list-style-type: none"> - Therapy of choice in hemodynamically unstable patients - Fewer hypotensive episodes - Possible earlier renal recovery - More effective management of marked fluid overload - Preferred in catabolic patients or patients with high protein requirements - Capacity to offer different modalities (SCUF, HDFVVC, HVHF) and different membranes and combination with sorbents 	<ul style="list-style-type: none"> - Advanced technology requiring specially trained health care personnel - Not available in all centers in Latin America - More expensive
PIRRT	<ul style="list-style-type: none"> - When CRRT is not available, it may be preferable in hemodynamically unstable patients - Same technology than IHD - Available in most centers across Latin America 	<ul style="list-style-type: none"> - Difficulty to adjust the dose of antibiotics
IHD	<ul style="list-style-type: none"> - Faster correction of biochemical abnormalities (acidosis, hyperkalemia, uremia, etc.) - Most common technology available - Available in all centers across Latin America 	<ul style="list-style-type: none"> - Frequent hypotensive episodes - May delay renal recovery
PD	<ul style="list-style-type: none"> - Less expensive - Lower risk of hypotension - Requires relatively less equipment, infrastructure, and resources - Available in most of the centers across Latin America - Automated PD, if available, permits faster and less labor-intensive correction of fluid overload 	<ul style="list-style-type: none"> - Increased contact between health care personnel and patients when frequent manual exchanges required - Can increase intra-abdominal pressure, interfere with respiratory mechanics - Use in a prone-positioned mechanically ventilated patient may be challenging
Adsorbents	<ul style="list-style-type: none"> - Cytokine removal 	<ul style="list-style-type: none"> - Expensive - Not available in all countries

Figure 6 : Comparison of available RRT techniques¹⁸

production of uremic solutes may outstrip the capacity of peritoneal dialysis to remove them.

Peritoneal dialysis has the added disadvantage of increasing intraabdominal pressure, which can increase the work of breathing and compromise respiratory mechanics.

One exception is with PD coupled with the use of an automated cycler to deliver it, which can increase the frequency of peritoneal dialysis cycles, thereby allowing usage of smaller volumes of dialysate and increasing clearance of solutes and removal of fluid.

Adequate nutrition is critical in the management of AKI in Covid-19. Prone position is compatible with enteral feeding²¹. Protein intake should be

- 1.3–1.5 g/kg per day in non-Dialysis AKI
- 1.0–1.5 g/kg per day in intermittent RRT
- 1.7 g/kg per day in CRRT

Renal Dosing of Commonly Used Drugs in Covid-19:

Dosing of Remdesivir in AKI/CKD: Remdesivir is a prodrug whose active metabolite has an intracellular half-life of around 20 hours. It is mostly excreted renally (75%), and toxicity is related to the carrier, a cyclodextrine (sulfobutylether- α -cyclodextrin sodium salt or SBECD). SBECD is cleared renally and accumulates when the GFR is < 30. It is associated with a form of AKI characterised by osmotic tubulopathy. SBECD is dialyzable²³ (around 50% removed by a standard 4-hour dialysis session). Small studies have shown Remdesivir is safe in ESRD populations. Most clinicians prefer to administer it after a session of dialysis.

Management of ESRD

In India, the Ministry of Health and Family Welfare (MOHFW) has released a document²⁵ entitled "Revised Guidelines for Dialysis of COVID – 19 patients", which provides guidance on how to go about performing dialysis safely in a Covid-19 pandemic.

Hemodialysis patients²⁶ are particularly at risk. Studies show that when HD patients suffer mortality

rates of 33 to 50 % when critically ill with Covid-19.

The goal of safe maintenance hemodialysis in a Covid-19 environment is to protect both patients and staff, avoid unnecessary exposure, and ensure adequacy of dialysis.

Every dialysis unit should have a “triage” area to identify possible Covid cases, where dialysis patients can have their temperature checked and also fill in/ answer a brief questionnaire pertaining to Covid symptoms.

Appropriate and adequate alternative arrangements should be in place for dialysis of covid patients and covid suspects.

The dialysis unit should be adequately stocked with masks, hand sanitiser and other protective equipment (gloves, N95 masks, face shield, goggles, protective gowns and respirator masks).

The usual trend in dialysis centres is to perform HD 2 to 3 times per week. To limit exposure, patients can be encouraged to limit HD to twice per week temporarily. To avoid getting into complications

from inadequate dialysis, such as fluid overload and hyperkalemia, it is essential to pay careful attention to sodium, potassium, and water intake, and to achieve strict control of blood pressure. The judicious use of high doses of diuretics can aid in managing volume and preventing hyperkalemia.

Reducing the frequency of dialysis can be risky in those who are anuric or have very little urine output- which is often the case in long-term dialysis patients or those who have glomerulonephritis as native kidney disease.

Now that effective vaccines are available, all patients and their attendants, as well as healthcare personnel working in dialysis units, should be encouraged to get a full course of vaccination.

All patients should be taught to recognise Covid symptoms in themselves and among their contacts. There should be non-punitive policies in place that encourage healthcare personnel to report their covid symptoms promptly.

Drug	Mechanism	Dose reported in COVID-19 trials	Dose adjustment in CKD?	Dose adjustment with KRT	Other considerations
Remdesivir	Nucleotide analogue, inhibits viral replication	200 mg x 1 then 100 mg daily	Excipient accumulates with GFR < 30 ¹	Potentially cleared ¹ Dose as if CrCl = Q _e Effluent	CrCl < 30 exclusion in most trials ¹ Likely high Vd since intracellular
Lopinavir/Ritonavir Kaletra	Protease inhibitors	400 mg / 100 mg twice daily	None	None	Both highly protein bound
Atazanavir Reyataz Ritonavir Norvir	Protease inhibitors	300 mg / 100 mg daily	None	None	> 80% protein bound
Darunavir Prezista /Ritonavir Norvir	Protease inhibitors	800 mg / 100 mg daily	None	None	Both highly protein bound
Favipiravir	Inhibits RNA polymerase	1200 mg twice daily for 2 days then 600 mg 2-3 times a day	?Yes	Potentially cleared Dose as if CrCl = Q _e Effluent	~50% protein bound
Tocilizumab	IL-6 antagonist	8 mg/kg (up to max 800 mg)	None	None	
Sarilumab Kevzara	IL-6 antagonist	150 - 200 mg	None	None	
Anakinra Kineret	IL-1R antagonist	100 mg daily	?every other day	None	
Colchicine	Inhibits microtubule polymerization; non-selective inflammasome inhibitor	0.5 mg twice daily ²	Yes ³	None	High volume of distribution; ~40% protein bound
Chloroquine/ Hydroxychloroquine Plaquenil	Block viral entry; immunomodulatory effects	CQ: 500 - 1000 mg a day (or 10 mg/kg) HCQ: 400 mg x 1 then 200 mg two or three times a day	None ³	None	~50-70% protein bound; high volume of distribution
Ivermectin	Nuclear transport inhibitor	Usually 0.2 mg/kg x 1	None	None	> 90% protein bound

Figure 7 : Renal Dosing of Covid therapies²²

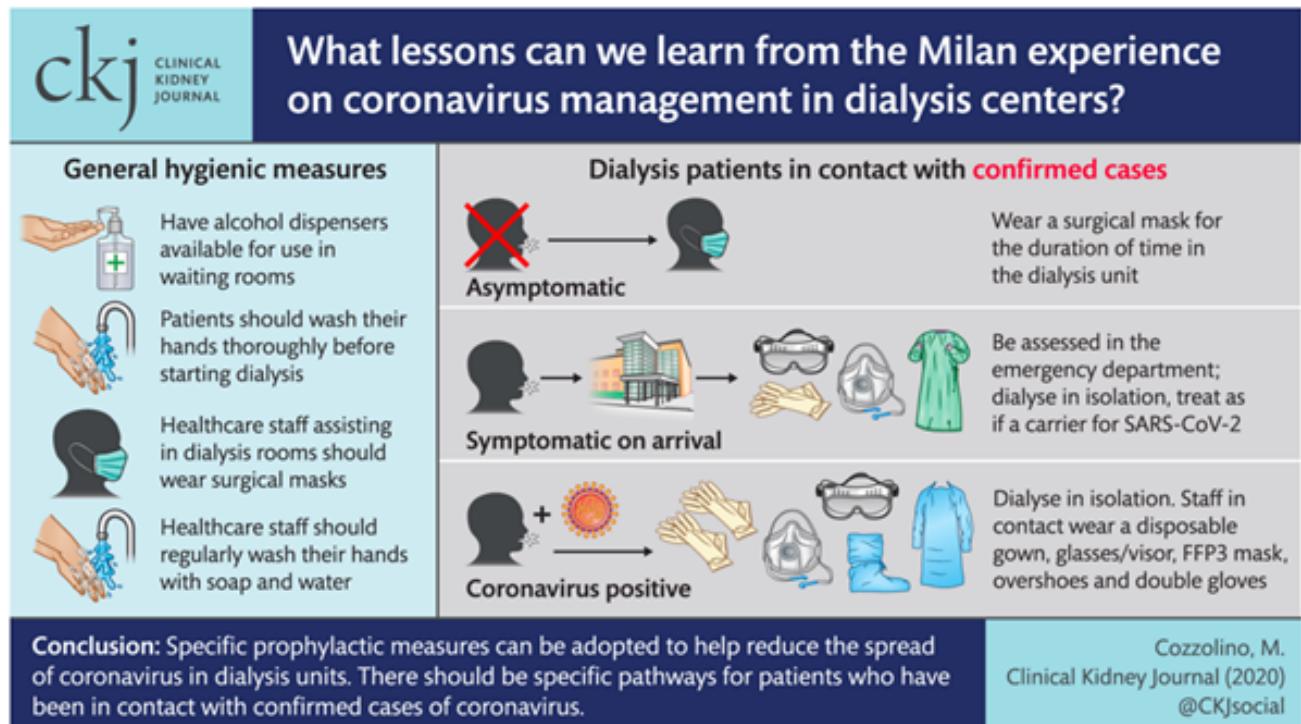


Figure 8: Management of dialysis centres

Dialysis patients should wear masks, and there should be a distance of at least 6 feet between beds. Similar distance should be maintained for seating arrangements.

In case there are no chairs or beds available, patients should be encouraged to wait in secure spaces elsewhere, even if it means waiting in an ambulance or personal vehicle until a bed becomes available in dialysis.

In theory, peritoneal dialysis is safer from a Covid viewpoint, but can run into severe logistical issues during lockdown. PD patients should be encouraged to maintain stock of at least 2 weeks of PD fluid, medications, and ancillary supplies at home.

Vascular surgeons and urologists who create AV fistulas for HD access should be encouraged to treat such procedures as essential.

Intravenous iron may exacerbate the inflammatory state, and most patients are resistant to erythropoietin during active Covid-19. These drugs should be withheld until recovery.

MANAGEMENT OF GLOMERULAR DISEASE

There is no specific treatment for COVAN.

Patients with non-Covid glomerular kidney disease

who are on immunosuppressive therapy are at increased risk for being infected and have a higher rate of mortality during Covid-19 illness.

In a newly diagnosed patient with glomerular disease who is at low risk of Covid-19 (can isolate, is fully vaccinated), one can plan immunosuppression as per usual guidelines.

Among patients who are at risk of Covid-19 and are newly diagnosed with glomerular disease, it is prudent to postpone immunosuppression if the clinical situation allows it. For example, patients with IgA Nephropathy or membranous nephropathy with proteinuria that suggests low risk of progression can be managed with conservative non-immunosuppressive therapy such as ACE inhibitors.

Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, do not increase the risk of Covid-19 and may even counteract cytokines such as IL-6, and it's safe to continue them if previously prescribed. Hydroxychloroquine has a similar safety profile.

It is prudent to avoid antimetabolites such as mycophenolate or azathioprine, cytotoxic drugs such as cyclophosphamide, and rituximab unless absolutely indicated. If the glomerular disease is in

remission and further immunosuppression can be minimised or stopped, one should take the opportunity to do so.

THE GLOMERULAR DISEASE PATIENT ON IMMUNOSUPPRESSION WHO DEVELOPS COVID-19:

Stop antimetabolites immediately and do not readminister until fully recovered. For patients on long term glucocorticoids and admitted with moderate to severe Covid-19, one should administer stress doses of steroids where indicated.

Management of Kidney Transplant

Kidney transplant recipients are at high risk for hospitalization and death²⁷ from COVID-19 (up to 28% in some studies). Kidney transplantation during a Covid pandemic is fraught with risks and uncertainties. During a pandemic, when cases are at a peak and healthcare resources are low, non-urgent transplants should be deferred until the case burden declines.

Patients who are waiting for a transplant should follow all Covid-safety protocols. Preferably they should have received their second dose of vaccine at least 2 weeks before transplant.

Potential kidney donors too should follow all safety protocols.

Before transplant, both donor and recipient should be screened by RT-PCR. The risk of infection from a non-lung organ being transplanted is extremely low, but nevertheless caution is warranted given the heavy immunosuppression recipients undergo. Cadaveric donors with unexplained respiratory failure as cause of death should not be considered for donation.

If a donor has been infected, they should wait for at least 3 weeks from time of diagnosis and for complete resolution of symptoms before being considered for donation. Donors who have been exposed to Covid should wait at least 2 weeks and have consecutive negative RT-PCR tests before donating a kidney.

Potential recipients who have been exposed to infection or have Covid-19 should wait until all symptoms have resolved and at least 2 consecutive RT-PCRs tests are negative before proceeding for

transplant.

Among kidney transplant recipients who develop Covid-19, fever is less likely, and lymphopenia is more severe, probably because of the anti-metabolite medications routinely used.

In moderate to severe Covid, one should temporarily withhold antimetabolite agents²⁸ (mycophenolate or azathioprine), particularly in the presence of lymphopenia.

Calcineurin inhibitors and m-TOR inhibitors can be continued. Stress doses of glucocorticoids may be necessary.

Many empirically used medications for Covid, such as azithromycin and hydroxychloroquine, can interact with CNI inhibitors and lead to dangerous prolongation of QT interval. All patients on such medications should have a screening ECG to rule out cardiac arrhythmias.

Tacrolimus and cyclosporine have synergistic nephrotoxicity when used with nephrotoxic medications like aminoglycoside antibiotics, amphotericin B and colchicine.

Drugs²⁹ that inhibit CYP3A metabolism and/or P-gp efflux, such as amiodarone, azole antifungals, and ART-boosting agents (e.g. ritonavir), macrolide antibiotics and non-dihydropyridine calcium channel blockers, can increase immunosuppressant serum concentrations, which can in turn cause renal dysfunction, hyperkalemia or accelerated hypertension. It may be prudent to adjust CNI dosages based on trough CNI levels.

Remdesivir and Casirivimab-imdevimab are safe to use in kidney transplant recipients.

Extracorporeal Therapies

Cytokine removal using adsorbent devices such as Cytosorb was in vogue during the pandemic but has not been proven in RCTs. They have no proven role now and should not be used outside a well-designed RCT.

Vaccination

Patients with kidney disease are at increased risk from COVID-19 and should be vaccinated unless absolutely contraindicated. Vaccines for other

diseases such as influenza can safely be administered concomitantly.

The immunogenicity of Covid vaccines is uncertain in immunosuppressed patients, but the benefits outweigh any potential risks.

Among the currently approved Covid vaccines in India, Covishield (AZD1222, ChAdOx1, Non-Replicating Viral Vector), and Sputnik V (Gam-COVID-Vac, Non-Replicating Viral Vector), as well as the mRNA vaccines (Pfizer and Moderna) which are not available in India, have been studied in CKD and dialysis patients in the original randomized trials.

Dialysis patients were excluded from the original RCT of Covaxin (BBV152, whole-virion α -propiolactone-inactivated SARS-CoV-2 vaccine).

However, there is now enough real-world experience to suggest all these vaccines can be used safely in CKD/dialysis patients

Dialysis patients should be prioritised for Covid vaccination, particularly those waitlisted for transplant.

Glomerular disease: Patients on immunosuppressive medication were excluded from RCTS with Covid vaccines, leading to a lack of data on long term safety and efficacy. Nevertheless, patients on immunosuppressive medication should be prioritised for Covid vaccines. Rituximab can abrogate the effect of Covid vaccine, so, if possible, it should be administered four to six weeks after completion of the COVID-19 vaccination³⁰³⁰ Clin. Exp. Immunol. 202, 149–161 (2020)

The US FDA has approved the use of a booster dose of mRNA vaccines for those on immunosuppressive medications.

In patients with active and severe glomerular disease, vaccination should be delayed to prioritize achievement of remission.

De novo glomerular disease can rarely occur post vaccination with mRNA vaccines, but the link is not proven to be causal at this point.

Vaccination in kidney transplant recipients should be delayed for at least one month post transplantation and for at least three months after the use of T cell-depleting agents (eg, anti-thymocyte

globulin) or B cell-depletion agents (Rituximab). These agents are commonly used as induction agents or to treat acute rejection in kidney transplantation.

Post AKI surveillance:

AKI is a known risk factor for the development of CKD. The AKI of Covid may only partially recover, setting the stage for CKD.

Many Covid patients experience development of de novo diabetes mellitus or worsening of glycemic control of existing diabetes, which can lead to deterioration of kidney function down the years. Hence, patients who have recovered from Covid and AKI should be monitored at regular intervals with urinalysis and renal function tests, and encouraged to manage their comorbidities to prevent kidney disease.

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Depression & Anxiety During the COVID-19 Pandemic



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Abstract:

The COVID-19 pandemic has resulted in an unparalleled challenge to public health and the health infrastructure. As evidenced by many studies the steps taken to contain the disease resulted in devastating economic and social disruption and has led to an increase in the incidence of depression, anxiety & suicide. The groups most commonly affected include patients with COVID-19, care givers and frontline health care providers.

AQ3: Keywords: Covid-19, Depression, Anxiety

Introduction

Mental health is defined by the World Health Organization (WHO), as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community"[1]. According to WHO, mental health includes "subjective well-being, perceived self-efficacy, autonomy, competence, intergenerational dependence, and self-actualization of one's intellectual and emotional potential, among others".[2]

The COVID-19 disease is caused by the highly transmissible Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-COV-2). It spread to pandemic levels globally in March 2020, resulting in significant mortality and morbidity. The disease has had an overwhelming effect on mental health. The psychological outcomes are seen at individual and community levels, including but not limited to fear of getting sick or dying, feeling of helplessness, and of being stereotyped. [3]

Though the data is still coming, the studies and surveys conducted during the Covid 19 pandemic consistently show an increased prevalence of

symptoms of depression, anxiety, Post Traumatic Stress Disorder (PTSD), and other forms of psychological distress such as emotional distress, stress, mood swings, irritability, insomnia, attention deficit hyperactivity disorder and anger [4, 5, 6].

Pathogenesis

A biopsychosocial model has been proposed to explain the pathogenesis of psychiatric illness. It is thought that the inflammatory immune response as a result of SARS-COV 2 infection may indirectly affect the central nervous system. The therapeutic interventions might also play a role.

The psychosocial factors include:

- Frequency and severity of the infection in the affected individual
- Fear of getting infected as also the fear of infecting relatives and colleagues
- Fear of not getting adequate medical care in case of infection
- Physical distancing and quarantine measures
- Increased workloads
- Financial adversity and uncertainty
- Shortages of available resources (eg, foods, paper products, and personal protective equipment)
- Unceasing media broadcasts about the pandemic and the ambiguity about the possible outcome

Depression

Depressive disorders are characterized by depressive mood (e.g., sad, irritable, empty) or loss of pleasure accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the individual's ability to function. Other symptoms include difficulty concentrating, feelings of

worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, somatic symptoms (like headaches, vague bodyache, etc) and reduced energy or fatigue. (ICD 11).

With a global estimated prevalence of approximately 5%, depression is among the foremost cause of disability(7). Depression can lead to suicide. Suicide is the fourth leading cause of death in 15-29-year-olds (8)

Women, young adults (ages 21yrs to 40 yrs), financial instability, low socioeconomic status, and exposure to the disease were found to be risk factors in most of the studies (9,10,11). The need for social isolation and the physical distancing requirements during the pandemic could have worsened the symptoms of depression(12). Exposure to social media was also associated with depression (13).

A survey conducted by Ettman CK *et al* in USA found that prevalence of depression symptoms US increased more than 3-fold during the COVID-19 pandemic, from 8.5% before COVID-19 to 27.8% during COVID-19.(14)

Metaanalyses by Juan Bueno-Notivol *et al* found that compared to the estimated global prevalence of depression (which was 3.44%), the current pooled prevalence is 7 times higher (25%).(15)

A cross-sectional study in Karnataka by Desai *et al* estimated the prevalence of depression to 47%. Depression was more in females and students (16). In a pan India electronic survey by S Verma and A Mishra, 25% of the participants had moderate to severe depression (17).

Majumdar et al., 2020 had reported that there was a rise in complaints of somatic discomfort. The participants who were mostly office workers and students complained discomfort in various parts of body. The probable reasons behind this rise in these symptoms during lockdown were physical inactivity, lack of routine in life, and an increased exposure to electronic gadgets.(18).

A metanalyses by Racine N *et al* concluded that pooled estimates obtained in the first year of the COVID-19 pandemic suggest that 1 in 4 youth

globally are experiencing clinically elevated depression symptoms, while 1 in 5 youth are experiencing clinically elevated anxiety symptoms. These pooled estimates, which increased over time, are double of prepandemic estimates. (19)

Many recent studies, both international and Indian, have reported that compared to general population, health care workers had higher incidence of psychological issues. In a review by DeKock *et al* (24 studies), the prevalence of depressive symptoms amongst health care workers ranged from 8.9% to 50.4% (20). A similar review by Salari *et al* (29 studies) estimated the prevalence of depression to be 40.4% in physicians and 28% in nurses(21).

The prevalence of depression was 35.4% and psychological distress was 57.5% in a metaanalysis of Indian studies among HCWs by RK Singh *et al.*(22)

It could have been due to increased workload, lack of safety equipment, fear of infecting family and colleagues, self-imposed quarantine and lack of family contact.

Anxiety / Fear

Anxiety and fear-related disorders are characterized by excessive fear and anxiety and related behavioural disturbances, with symptoms that are severe enough to result in significant distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. It is manifested by either general apprehension (i.e. 'free-floating anxiety') or excessive worry focused on multiple everyday events, most often concerning family, health, finances, and school or work, together with additional symptoms such as muscular tension or motor restlessness, sympathetic autonomic over-activity, subjective experience of nervousness, difficulty maintaining concentration, irritability, or sleep disturbance. (ICD 11)

A metaanalysis of community based studies by J Santabarbara et al found that the overall prevalence of anxiety was 25%. Also the reported risk factors for the development of anxiety included initial or peak phase of the outbreak, female sex, younger age, marriage, social isolation, unemployment and

student status, financial hardship, low educational level, insufficient knowledge of COVID-19, and epidemiological or clinical risk of disease(23).

The prevalence of anxiety was 31.9% in a metanalysis by Salari *et al.* (21) According to Verma and Mishra, the prevalence of anxiety was 28%, (17) whereas it was 41.5% in a study in Karnataka (Desai *et al*)[16]. It was more in women and young adults in the age group 21 – 25 yrs (Kazmi *et al*) (24).

The possible causes for increase in anxiety could be the uncertainty, disruptions in daily routines, and concerns for the health and well-being of family and loved ones during the COVID-19 pandemic.

A crosssectional online survey among HCWs in India by Wilson *et al.*, 2020 showed moderate and high level of stress in 81% participants and moderate and severe anxiety in 17.7% respondents(25). A systemic review (Gupta and Sahoo. 2020) showed that 37% of frontline health care providers had symptoms of anxiety(26). The prevalence of anxiety was 35.3% and psychological stress was 65.1% among HCWs in a metaanalysis of Indian studies. (22)

Conclusion

SARS-COV2 triggered lockdowns, social distancing, quarantines, widespread acute illness and death have a negative impact which leads to fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. Fear of contracting the virus, experiences of bereavement, and uncertainty about the future have compounded these stressors.

The repercussions of the disease are intense psychological and social stressors, severely impacting mental health leading to increases in anxiety and depression, self-harm and suicidal behaviours, especially the vulnerable section of society.

Recommendations

To mitigate the risk of developing psychiatric illness:

- Use only reliable sources of information.
- Avoid excessive social media use as it can increase the exposure to 'fake' news and

rumours.

- Adhere to safety measures like distancing and hand hygiene as these are proven methods for avoiding the infection.
- Take regular breaks in daily routine with activities like meditation, music, yoga, etc.
- Cultivate hobbies and routines.
- Exercise regularly.
- Acknowledge and share feelings and emotions.
- Do not hesitate to consult a psychiatrist.

Conflict of interest: None

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COVID 19 and Diabetes Mellitus

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019. As of 4th November 2021, 247.5 million globally confirmed cases of COVID-19 and 5.01 million deaths [Ref: World Health Organization COVID-19 dashboard]. The fatality rate for COVID-19 has been estimated to be 0.5–1.0% [1–3]. SARS-CoV-2 is a positive-stranded RNA virus that is enclosed by a protein-decorated lipid bilayer containing a single-stranded RNA genome. SARS-CoV-2 has 82% homology with human SARS-CoV, which causes severe acute respiratory syndrome (SARS) [4]. In human cells, the main entry receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) [5] which is highly expressed in lung alveolar cells, cardiac myocytes, vascular endothelium and various other cell types [6].

Patients at high risk of severe COVID-19 or death have several characteristics, such as advanced age and male sex, and underlying health issues, such as cardiovascular disease (CVD), obesity and/or type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) [7–9]. A few early studies have shown that underlying CVD and diabetes mellitus are common among patients with COVID-19 admitted to ICUs [10,11]. International Diabetes Federation estimated that in 2019–2020 there were 463 million people living with diabetes. The presence of diabetes mellitus and the individual degree of hyperglycemia seem to be independently associated with COVID-19 severity and increased mortality [12,13]. The presence of typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increases COVID-19 mortality [14].

RISK OF SEVERE COVID-19

Severe illness is manifested as the need for hospitalization, intubation and death. Risk of severe illness is most pronounced in adults with advanced age or underlying medical comorbidities, including diabetes [15]. Patients with Type 2 diabetes are more likely to have serious complications, more intensive care unit (ICU) admissions and longer length of stay and death from COVID-19 [16]. In the population cohort study from the United Kingdom, patients with type 1 diabetes also had an increased risk of in-hospital mortality compared with the general population without known diabetes [17]. The United Kingdom study did not report data on people with type 1 diabetes age 49 or younger due to privacy concerns related to small sample size. Therefore, there are limited data in this population, although, if infected, they are likely to have a more prolonged course than similarly healthy people without type 1 diabetes, as is seen in other infections [18].

ROLE OF HYPERGLYCEMIA

Poorly controlled diabetes is a risk factor for infection in general. Since COVID-19 can trigger an intense inflammatory response, it has been challenging to disentangle whether hyperglycemia in COVID-19 is a cause, or, as appears more likely, a consequence of severe disease. Factors, other than obesity, older age, and associated comorbidities, such as differential expression of angiotensin-converting enzyme (ACE) receptors or other molecular mechanisms, may play a stronger role in COVID-19 outcomes among patients with diabetes [19]. An analysis done in over 10,000 COVID-19-related deaths in people with diabetes [predominantly type 2] of national diabetes and mortality data from the United Kingdom before and during the pandemic showed an association

between preceding hyperglycemia and mortality. In type 2 diabetes mortality risk was higher with glycated hemoglobin (A1C) 7.6 to 8.9 percent compared with 6.5 to 7 percent (hazard ratio [HR] 1.22 [95% CI 1.15-1.30]) and increased as A1C levels rose. In type 1 diabetes mortality risk was significantly higher with A1C >10 percent (86 mmol/mol) compared with 6.5 to 7 percent (HR 2.23 [95% CI 1.50-3.30]).

CLINICAL PRESENTATIONS

COVID-19 infection appears to precipitate severe metabolic manifestations of diabetes, including diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and severe insulin resistance [20]. COVID-19 infection appears to precipitate severe metabolic manifestations of diabetes, including diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and severe insulin resistance [20]. Patients may or may not have a history of diabetes [21]. In a systematic review of 19 reports (110 patients with DKA or HHS) only 77 % of patients had pre-existing diabetes [22]. Less severe presentations of newly diagnosed diabetes have also been reported. In a systematic review of eight retrospective cohort studies (3700 patients with severe COVID-19), diabetes was newly diagnosed in 0.6 to 62 percent [23]. Newly diagnosed hyperglycemia may be due to critical illness per se, or there may be direct beta cell injury from SARS-CoV-2 or from the inflammatory response to the virus [24].

POTENTIAL PATHOGENIC MECHANISMS IN PATIENTS WITH DM AND COVID-19

Infection with (SARS-CoV-2) leads to increased levels of inflammatory mediators in the blood, increased interstitial and/or vascular permeability for pro-inflammatory products by modulation of natural killer cell activity and IFN α production. Increased reactive oxygen species (ROS) production and leads to lead to lung fibrosis, acute lung damage and ARDS. ROS production and viral activation of the RAAS cause insulin resistance hyperglycaemia and vascular endothelial damage. All of them contribute to cardiovascular events, thromboembolism and disseminated intravascular coagulation (DIC). Infection also causes increases in the clotting

components fibrinogen and D-dimer leading to increase in blood viscosity and vascular endothelial damage and thus associated with cardiovascular events, thromboembolism and DIC [25].

COVID-19 AND GLUCOSE METABOLISM

In human monocytes elevated glucose levels directly increase SARS-CoV-2 replication and glycolysis sustains SARS-CoV-2 replication via the production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor 1 α (HIF 1 α) [26]. Therefore, hyperglycaemia might support viral proliferation. In accord with this assumption, hyperglycemia or a history of T1DM and T2DM were found to be independent predictors of morbidity and mortality in patients with SARS [27]. Patients with diabetes mellitus typically fall into higher categories of SARS-CoV-2 infection severity than those without [28,18]. Poor glycaemic control predicts an increased need for medications and hospitalizations, and increased mortality [29]. It was also noted that glycaemic deterioration is a typical complication of COVID-19 in patients with impaired glucose regulation or diabetes mellitus. For example, in patients requiring insulin, SARS-CoV infection was associated with a rapidly increasing need for high doses of insulin (often approaching or exceeding 100 IU per day) [30]. Changes in insulin needs are seemingly associated with the levels of inflammatory cytokines [30,31].

INFLAMMATION AND INSULIN RESISTANCE

The most common post-mortem findings in the lungs of people with fatal COVID-19 are diffuse alveolar damage and inflammatory cell infiltration with prominent hyaline membranes [32]. Other critical findings include myocardial inflammation, lymphocyte infiltration in the liver, macrophage clustering in the brain, axonal injuries, microthrombi in glomeruli and focal pancreatitis [32]. An integrated analysis showed that patients with severe COVID-19 have a highly impaired interferon type I response with low IFN α activity in the blood, indicating high blood viral load, and an impaired inflammatory response [33]. Some patients with severe COVID-19 experience a cytokine storm, which is a dangerous and potentially life-threatening event [34,35]. A retrospective study of 317 patients with laboratory-

confirmed COVID-19 showed the presence of active inflammatory responses (IL-6 and lactate dehydrogenase) within 24 h of hospital admission, which were correlated with disease severity [36]. Blood levels of IL-6 and lactate dehydrogenase are independent predictors of COVID-19 severity [36]. Several mechanisms have been proposed by which virally induced inflammation increases insulin resistance [37]. In coronavirus-induced pneumonia, such as SARS and MERS, inflammatory cells infiltrate the lungs, leading to acute lung injury, ARDS and/or death [38]. This large burden of inflammatory cells can affect the functions of skeletal muscle and the liver, the major insulin-responsive organs that are responsible for the bulk of insulin-mediated glucose uptake [39]. In addition, patients with severe COVID-19 show muscle weakness and elevation of liver enzyme activities, which might suggest multiple organ failure, particularly during a cytokine storm [40].

IMMUNOMODULATION

It is recognized that mechanisms linking COVID-19 and both T1DM and T2DM overlap with pathways that regulate immune function [41]. T2DM is associated with immunological dysregulation, which is potentially equivalent to accelerated ageing, and could therefore potentially explain the poor prognosis in patients with diabetes mellitus and COVID-19 [42,43]. Individuals with impaired glucose tolerance or diabetes mellitus have reduced NK cell activity [44,45,46]. That explains why patients with diabetes mellitus are more susceptible to COVID-19 and have a worse prognosis than those without diabetes mellitus.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE2 has already received much attention as it can also serve as an entry receptor for SARS-CoV as well as SARS-CoV-2 [47]. ACE2 was initially reported to be predominantly expressed in the respiratory system [47]. However, a more sophisticated study using immunohistochemical analyses found that ACE2 is expressed mainly in the intestines, kidneys, myocardium, vasculature and pancreas, but expression is limited in the respiratory system [48]. ACE2 is considered an important SARS-CoV-2 receptor facilitating infection of relevant cells, such

as pneumocytes. Evidence suggests an association between ACE2 and glucose regulation [49]. Infection with SARS-CoV can cause hyperglycaemia in people without pre-existing diabetes mellitus [50]. This finding and the localization of ACE2 expression in the endocrine pancreas together suggest that coronaviruses might specifically damage islets, potentially leading to hyperglycaemia [50]. These data suggest that the ACE2 as part of the RAAS might be involved in the association between COVID-19 and diabetes mellitus.

INCREASED COVID-19 SEVERITY

The patients with T2DM have high prevalence, severity of disease and mortality during Covid-19 infection. In the large cohort by Guan et al. the 15.7% of patients presented with severe disease. The rates of severe disease were significantly higher in patients with diabetes compared with non-diabetes (34.6% vs. 14.2%; p<0.001). Similarly, 6.1% of patients experienced the composite endpoint, that was again significantly higher among diabetic vs. non-diabetic patients (22.2% vs. 4.8%; p<0.001). 2 early case series of critically ill patients with COVID-19 admitted to ICUs in the USA found diabetes mellitus prevalence of 58% and 33% [51,52]. Glucotoxicity, endothelial damage by inflammation, oxidative stress and cytokine production contribute to an increased risk of thromboembolic complications and of damage to vital organs in patients with diabetes mellitus [53]. Drugs often used in the clinical care of patients with covid-19, such as systemic corticosteroids or antiviral agents, might contribute to worsening hyperglycaemia.

POTENTIAL ACCENTUATED CLINICAL PROCESSES AFTER SARS-COV-2 INFECTION IN PATIENTS WITH DIABETES MELLITUS

SARS-CoV-2 infection increases metabolic rate, resulting in tissue hypoxia, which induces interstitial lung damage and acute respiratory distress syndrome. Patients with diabetes mellitus and COVID-19 exhibit dysregulation of glucose homeostasis, aggravation of inflammation and impairment in the function of the immune system. These conditions increase oxidative stress, cytokine production and endothelial dysfunction leading to increased risk of thromboembolism and damage

to vital organs. All these factors contribute to increased severity of COVID-19 and rapid progression to cardiorespiratory failure in patients with diabetes mellitus [25].

EFFECT OF GLUCOSE LOWERING DRUGS ON COVID—19

Concomitant anti-diabetic therapy may affect pathogenesis of COVID-19 and, thus, have implications on the management of patients with COVID-19 and diabetes.

Metformin – Use of metformin has been associated with significantly reduced mortality in patients with COVID-19. The effectiveness of metformin has been shown to be higher in non-hospitalized patients compared to hospitalized patients. This might be due to an increased risk of side effects i.e., metabolic acidosis in hospitalized patients leading to discontinuation of the drug in these patients and switch-over to insulin. The possible mechanisms for these beneficial effects may be inhibition of cytokine storm via suppression of interleukin-6 (IL-6) signalling, preventing the process of lung fibrosis, suppressing endocytosis, and thereby elevating angiotensin converting enzyme 2 (ACE2) expression. Metformin also inhibits the cytokine production of pathogenic Th1 and Th17 cells. It may have additional benefits through reduction of production of proinflammatory cytokines using macrophages and by formation of neutrophil extracellular traps (NETs). [25]

Thiazolidinediones - In multiple studies, they have been found to reduce insulin resistance and to have putative anti- inflammatory and antioxidant effects, contributing to their anti-atherosclerotic properties. On the other hand, thiazolidinedione therapy is associated with weight gain and oedema and more importantly was associated with aggravation of heart failure. Thus, more clinical trials are needed to optimize the risk–benefit ratio of using thiazolidinediones in patients with COVID-19. [25]

DPP4 inhibitors – DPP4, also known as CD26, is a part of immune system and it regulated expression of many chemokines. DPP4 was involved in the pathogenesis of MERS-COV-2 as it mediated the entry of the viral particles into the host cell. No data has shown any such role of DPP4 in the

internalization of SARS-COV-2 and more research is required in this respect. In a retrospective case-control study from northern Italy, sitagliptin treatment during hospitalization was associated with reduced mortality and improved clinical outcomes in such patients. However, in meta-analyses, it has been shown to reduce the mortality non-significantly or has been associated with poor outcomes. Thus, at present, more prospective studies are required in patients with T2DM and COVID-19 to assess the potential survival benefits associated with DPP4 inhibition in patients with COVID-19. [25]

GLP1 analogues – These drugs have significant anti-inflammatory and anti-adipogenic effects, thus decreasing insulin resistance. The anti-inflammatory effect may be mediated through reduced macrophage infiltration via GLP1 signalling and by reduction of TNF- α and IL-6. People with CVD or kidney disease show a worse prognosis during the course of COVID-19 than those without these diseases. Beneficial effects of GLP1 analogues on cardiac and renal systems are well established and it would be prudent to use these drugs in patients with COVID-19 with such risk. Obesity is itself a major risk factor for mortality in patients with COVID-19 and the weight reducing properties of GLP1 analogies makes them a suitable treatment in such patients with COVID-19. [25]

SGLT2 inhibitors – Gliflozins have cardiovascular and renal benefits through multiple mechanisms. Despite these benefits, there are concerns about gliflozins use in COVID-19 because of their propensity to cause volume contraction, renal insufficiency and increased risk of ketoacidosis, especially in hospitalized patients. As such, the use of SGLT2i might be difficult in patients under critical care, who need meticulous control of their fluid balance. In addition, these drugs must be discontinued in the face of a reduced estimated glomerular filtration rate, which limits their glucose- lowering effects substantially.

The choice of agents should be guided mainly by their presumed effectiveness and by their adverse effects. At present, in line with recommendations from Drucker [55], DPP4is and GLP1 analogues may be used in patients with mild to moderate

symptoms because these agents have proven glucose-lowering efficacy in hospital settings, as well as in outpatient clinics. For critically ill patients, there is insufficient data to recommend any of the classes of drugs other than insulin, which forms the mainstay of treatment in such patients. Specific recommendations for the treatment of ketoacidosis in patients with COVID-19 have been published, with an emphasis on subcutaneous insulin regimens. Frequent blood glucose and ketone body monitoring is mandatory in patients with COVID-19 and hyperglycaemia. Fluid and electrolyte management in patients with COVID-19 and impaired respiratory function should follow general recommendations.

COVID-19 TREATMENTS AND GLYCEMIC CONTROL

Antiviral therapies

Camostat Mesilate is a potent serine protease inhibitor. It is being researched for its ability to block the entry of SARS-CoV-2 into host cells. It has previously been shown to reduce the incidence of newly diagnosed diabetes in patients with chronic pancreatitis. The antimalarial drugs chloroquine and hydroxychloroquine have been used to treat SARS-CoV-2 infection on a large scale. In addition to their proposed antiviral actions against SARS-CoV-2 and anti-inflammatory effects, they have glucose-lowering efficacy by increasing insulin sensitivity and improving pancreatic α -cell function. Protease inhibitors (lopinavir, ritonavir) have been shown to reduce insulin sensitivity and glucose disposal thereby causing hyperglycemia and new onset diabetes mellitus. In animal studies, remdesivir, a nucleotide analogue inhibitor of RNA-dependent RNA polymerase, was shown to improve hyperglycaemia, insulin resistance, fatty liver and endotoxemia.

Adjunctive therapies

Systemic corticosteroids are one of the common agents causing hyperglycaemia, primarily by increasing postprandial levels of glucose, insulin resistance and pancreatic α -cell dysfunction, that often necessitates the initiation of insulin therapy. In spite of its adverse effect on glycemic control, meta-analysis of clinical trials showed that systemic

corticosteroid therapy is associated with reduced short-term all-cause mortality in patients with severe COVID-19.

COVID AND NEW ONSET DIABETES MELLITUS

A number of studies have reported new-onset diabetes mellitus that phenotypically could be classified as either T1DM or T2DM as being associated with the presence of COVID-19. A study from London, U.K., reported 30 children aged 23 months to 16.8 years with new-onset T1DM^[54]. Of these, 70% presented with diabetic ketoacidosis (DKA), 52% with severe DKA, and 15% with a positive COVID-19 test^[55]. The authors concluded that this represented an 80% increase in new-onset T1D during the pandemic compared with previous years^[55]. Further, it would also appear that the severity of presentation of youth with T1D is increased^[56]. Conflicting results have also been reported, however, with data from 216 pediatric diabetes centers in Germany showing no increase in the number of children diagnosed with T1D during the early months of the pandemic^[57]. However, the same centers reported data on 532 children and adolescents with newly diagnosed T1D and found significant increases in DKA and severe ketoacidosis at diagnosis during the same time period^[58]. In a study from Wuhan, China, patients with newly diagnosed diabetes were more likely to be admitted to the intensive care unit, require invasive mechanical ventilation, have a high prevalence of acute respiratory distress syndrome, acute kidney injury, or shock, and have the longest hospital stays^[59]. The study also reported data showing that glucose levels at hospital admission in people with newly diagnosed diabetes and in those with a history of diabetes were both associated with the increased risk of all-cause mortality^[59]. Patients with newly diagnosed diabetes had a higher mortality than COVID-19 patients with known diabetes, hyperglycemia (fasting glucose 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%) or normal glucose (HR 9.42)^[59].

It is currently unclear whether the new onset diabetes associated with COVID-19 is type 1, type 2, or a complex subtype of diabetes. Although in T1D insulin deficiency is usually the result of an autoimmune process, in SARS-CoV-2 infection it

could be due to destruction of the B-cells. Unfortunately, studies of islet cell antibodies in people with new-onset diabetes have been limited to a few case reports [60,61]. One study of hospitalized patients with SARS-CoV-1 infection showed that immunostaining for angiotensin-converting enzyme 2 (ACE2) protein was strong in pancreatic islets but weak in exocrine tissues [62]. However, a recent study from India compared new-onset diabetes in hospitalized patients prior to COVID-19 with new-onset diabetes during COVID-19 [63].

COVID-19 and TYPE1 DM

Newly diagnosed T1DM- Case reports have described patients with newly diagnosed T1DM with ketoacidosis occurring at the onset of COVID-19 and without ketoacidosis in whom ketoacidosis occurred several weeks after apparent recovery from COVID-19 [64,65]. These findings raise the question as to whether SARS-CoV-2 can trigger this metabolic disease. Studies from UK and Italy had contradictory findings that might be explained by

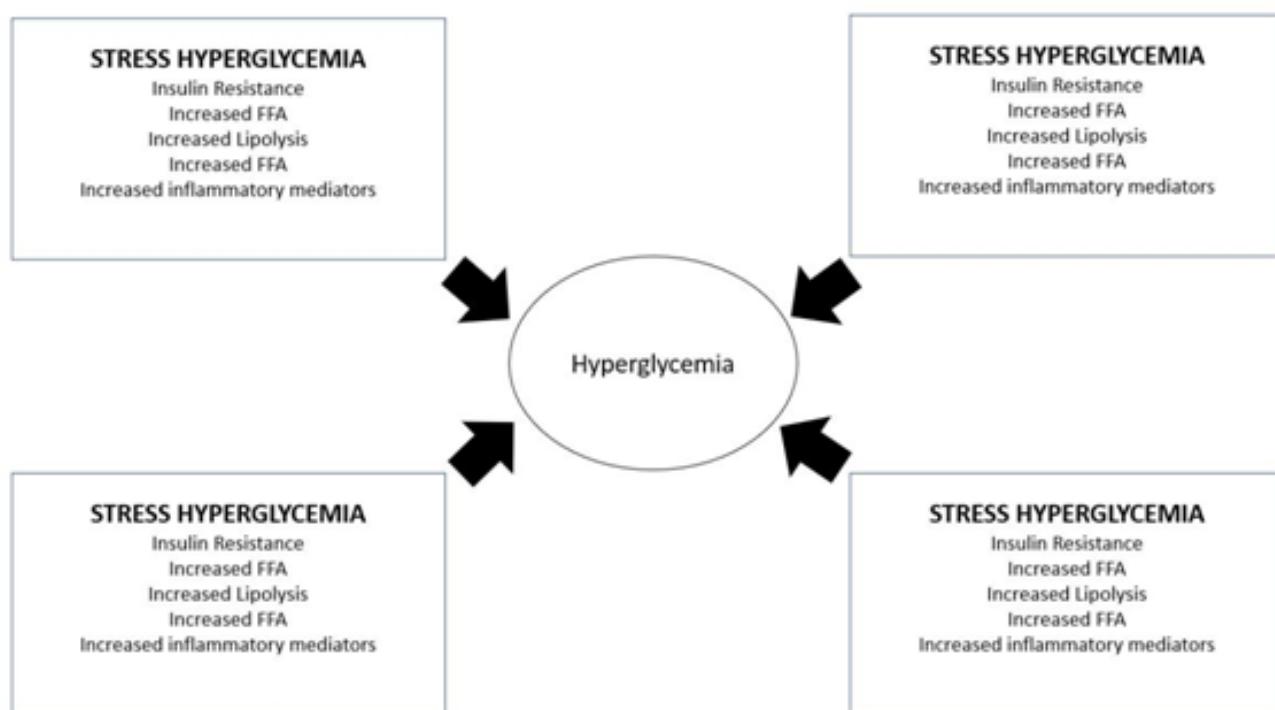


Figure 1 - Potential mechanisms for new-onset diabetes

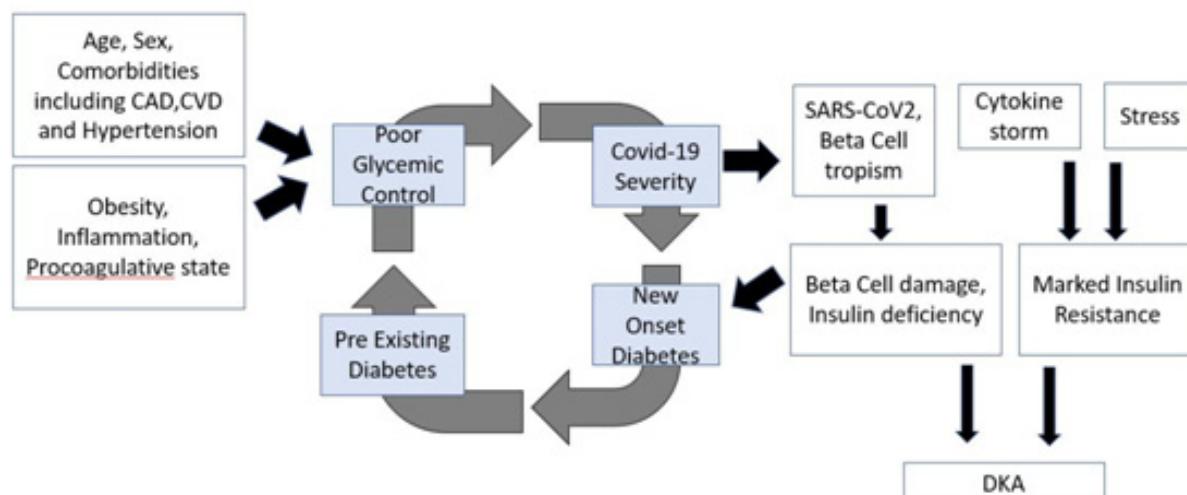


Figure 2 : Bidirectional relationship between T2DM, Hyperglycemia & Covid-19

the small patient numbers analysed [66,67,68]. A population-based study from Germany found no deviation from the projected numbers of newly diagnosed pediatric patients with T1DM [69]. However, the same study found a statistically significant increase in diabetic ketoacidosis and severe ketoacidosis in children and adolescents presenting with new-onset T1DM [70]. A probable explanation is that this finding reflects patients trying to delay hospital admission because of their fear of acquiring SARS-CoV-2 infection. As the COVID-19 pandemic progresses and larger numbers of patients are studied, it will become more apparent if a true link exists between COVID-19 and new-onset T1DM.

HOSPITALIZED PATIENTS WITH T1DM AND COVID-19

A population-based analysis from Belgium showed a similar risk of hospitalization in people with T1DM than in normoglycemic individuals (0.21% vs 0.17%) [71]. In this study and another from the USA hospitalized patients with T1DM being treated for COVID-19 had metabolic characteristics similar to patients with T1DM who were hospitalized owing to other diagnoses and the levels of HbA1c were not higher in the patients with COVID-19. However, plasma concentrations of glucose at the time of admission in patients were higher with T1DM and COVID-19 than in patients without non-COVID-19 diagnoses, indicating some acute deterioration in glycemic control.

THROMBOEMBOLIC EVENTS

Evidence suggests that COVID-19 considerably increases the likelihood of thromboembolic events, which represent a predominant cause of death [72,73]. Vascular endothelial dysfunction seems to contribute to the pathophysiology of microcirculatory changes in patients with SARS-CoV-2 infection [74]. Importantly, SARS-CoV-2 can enter and infect endothelial cells via the ACE2 receptor [75], with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis and microvascular prothrombotic effects [76]. Post-mortem examinations of patients who died with SARS-CoV-2 infection have demonstrated viral inclusions within endothelial cells and sequestered mononuclear and

polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis [78]. Thus, evidence suggests that an increased release of coagulation factors and dysregulation and destruction of the endothelial cells are the main mechanisms of the increase in thromboembolism in patients with COVID-19 [77]. Endothelial dysfunction might also explain reports of cerebrovascular complications in younger patients, and in patients with myocardial ischaemia and/or thromboembolic complications [78,79].

Population-based studies found that patients with T2DM exhibited an increased risk of venous thromboembolism compared with controls (HR 1.44) [80]. Furthermore, the risks of pulmonary embolism were greater in the patients with T2DM than in the controls (HR 1.52) [81]. Another study found that the incidence of deep vein thrombosis (DVT) after total knee replacement was statistically significantly higher in patients with diabetes mellitus [81].

COVID VACCINE AND DM

With clinical data supporting a robust neutralizing antibody response in COVID-19 patients with DM, vaccination in individuals with DM is justified [82]. In fact, as the burden of the disease is borne by people with DM, COVID-19 vaccination should be prioritized in individuals with DM [82]. The prognosis of people with diabetes affected by COVID-19 is particularly bad [83]. This reality raises the claim for prioritizing the vaccination against SARS-CoV-2/ COVID-19 in people with diabetes [83]. Only a few cases have been reported with New Onset DM after Covid Vaccine. Abu-Rumaileh MA et al has reported report a case of new-onset diabetes type 2 presenting as hyperosmolar hyperglycemic state (HHS) in a patient after receiving COVID-19 vaccine [84].

MUCORMYCOSIS

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, during a period of 2019–2020. India has highest cases of the mucormycosis in the world. Notwithstanding, India is already having second largest population

with diabetes mellitus (DM). Importantly, DM has been the most common risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and the USA [85].

DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46%. There is increasing case reports of Rhino-Cerebral Mucormycosis in people with COVID-19, especially in India. Diabetes mellitus (DM) is an independent risk factor for both severe COVID-19 and mucormycosis. Presence of DM was an independent risk factor (Odds ratio [OR] 2.69; P < 0.001) in a large 2018 meta-analysis of 851 cases [85].

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an Ideal environment of low oxygen (hypoxia), high glucose level, High iron levels (increased ferritins), Decreased phagocytic activity of WBC due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) & Prolonged hospitalization with or without mechanical ventilators.

Increase in Mucormycosis in Indian context appears to be unholy intersection of trinity of diabetes (high prevalence genetically), rampant use of corticosteroid (increases blood glucose and opportunistic fungal infection) and COVID-19 (cytokine storm, lymphopenia, endothelial damage). All efforts should be made to maintain optimal hyperglycemia and only judicious evidence-based use of corticosteroids in patients with COVID-19 is recommended in order to reduce the burden of fatal mucormycosis.

COVID AND ENDOTHELIUM; A SEQUELAE

The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial dysfunction - a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state [86]

Mounting evidence suggests that loss of vessel barrier integrity and the development of a pro-coagulative endothelium contributes to the initiation and propagation of ARDS in COVID-19, by inducing endothelitis and mediating inflammatory cell infiltration in the lungs. SARS-CoV-2 may alter vascular homeostasis by directly infecting endothelial cells via ACE2.

Additional mechanisms, have also been proposed as key pathogenic processes underlying endothelial dysfunction following SARS-CoV-2 infection such as a reduction of endothelial nitric oxide synthase activity and nitric oxide levels, as well as the release of vascular endothelial growth factor (VEGF) as a consequence of the systemic hypoxia induced by ARDS.

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Covid and the Eye

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The Coronavirus disease (COVID-19) first reported in late 2019 in Wuhan, China swiftly spread across the world and was declared a global pandemic on March 11, 2020 [1]. It is caused by the highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Apart from the systemic manifestations, various ocular manifestations have been reported. Initially there were several reports of eye redness and irritation in COVID-19 patients suggesting conjunctivitis is an ocular manifestation of SARS-CoV-2 infection. This conjunctivitis may be the harbinger of COVID-19 disease in some patients making the treating Ophthalmologist the first to suspect a coronavirus infection. Indeed, one of the first medical professional to voice concerns regarding the spread of coronavirus in Chinese patients was Dr. Li Wenliang, MD, an Ophthalmologist. He later died from COVID-19 and was believed to have contracted the virus from an asymptomatic glaucoma patient in his clinic. This highlights the need for understanding the ocular signs and symptoms, their management and safety protocols to prevent spread of the disease [1]

Epidemiology

Currently the total estimated numbers of affected cases are 229,010,902 out of which 33,448,163 are in India with about 444,869 deaths in India due to COVID-19 disease [2].

Early studies postulated that ocular manifestations were rare overall. Only 9 (0.8%) out of 1099 patients from 552 hospitals across 30 provinces in China were reported to have "Conjunctival congestion" from December 2019 through January 2020 [3]. More recent data, however have reported a much higher incidence of ocular signs and symptoms.

The pooled prevalence of all ocular manifestations among COVID-19 patients was 11.03 % (95% CI:5.71-17.72) according to a meta-analysis by Nasiri et al. [4] The most prevalent ocular manifestations were dry eye or foreign body sensation (n = 138, 16.0%), redness (n = 114, 13.3%), tearing (n = 111, 12.8%), itching (n = 109, 12.6%), eye pain (n = 83, 9.6%), and discharge (n = 76, 8.8%). The most prevalent ocular disease was conjunctivitis (n = 79, 88.8%).

Etiopathogenesis

Coronaviruses (CoVs) have caused three large-scale outbreaks over the past two decades: severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and now COVID-19. The origin of the COVID-19 pandemic was traced back to a cluster of pneumonia cases connected to a wet seafood market in Wuhan City, Hubei Province, China. Following the likely spillover of a zoonotic disease, further work confirmed the etiological agent to be a novel Betacoronavirus genus, group 2 [Fig 1 see Color pages section] related to SARS-CoV. CoVs of the family Coronaviridae are enveloped, positive-sense single-stranded RNA viruses [5]. The spike protein (S) in the structure has a receptor binding domain (RBD) that mediates direct contact with a cellular receptor, angiotensin converting enzyme (ACE2). Efficient cell entry requires cleavage by protein transmembrane serine protease 2 (TMPRSS2). ACE 2 is expressed primarily on respiratory mucosal and alveolar epithelial cells and has been identified in other tissues, including the gastrointestinal tract, kidney, vascular endothelial cells, immune cells, and even neurons. Virulence is achieved via direct cellular invasion and death and the induction of widespread cytokine-driven inflammation and vascular leakage. [6]

The possibility of infection through ocular secretions is being explored. The theories supporting the hypothesis of spread of COVID 19 infection through ocular secretions are

1. Direct inoculation of ocular tissue from respiratory droplets or aerosolized virus particles
2. Migration from nasopharynx via nasolacrimal duct
3. Hematogenous spread through lacrimal gland [7]

Data surrounding the expression of ACE2 and TMPRSS2 on the ocular surface are mixed. Lange et al found the human conjunctiva to have low levels of ACE2 [8]. A case report from Italy isolated SARS-CoV-2 by RT-PCR from conjunctival swabs on day 21 and day 27 after it was negative by nasopharyngeal swab [9]. Since SARS-CoV-2 hasn't been successfully cultured from human tears or conjunctival swab, the viability and transmissibility of SARS-CoV-2 in human ocular secretions remains uncertain [10]. Some reports suggest that tears can be source of transmission of infection, both early and late in the disease, even after patient becomes asymptomatic [11]. It has been postulated that the deceased Ophthalmologist, Dr. Li Wenliang of Wuhan, China may have contracted the infection via ocular transmission [12]. A figure representing the confirmed and suspected modes of transmission is shown below [Fig 2 see Color pages section]

OCULAR MANIFESTATIONS OF COVID-19

Eyelid and Anterior segment manifestations

Conjunctivitis is the most common ophthalmic manifestation documented in COVID 19 patients. Sen et al, in their review article found 120 patients with ocular surface and corneal signs and symptoms. The median gap between COVID 19 symptom/diagnosis and ophthalmic findings was 8.5 (mean 11.1 ± 8.8 , 2–32) days. But it was the initial or concurrent presentation in 12/26 published articles [13]. The symptoms were eye redness, ocular irritation, eye soreness, foreign body sensation, tearing, mucoid discharge, eyelid swelling, congestion and chemosis.

A. Follicular conjunctivitis

Sindhuja et al., in their large case series of patients with mild COVID-19 infection, reported that 11/127 (8.66%) had conjunctivitis [14]. Chen et al. suggested that ocular manifestations are more common in the middle phase of the disease based on their findings of bilateral acute follicular conjunctivitis in a patient on the 13th day of the illness [15]. Nayak et al. reported delayed onset of follicular conjunctivitis four weeks after severe COVID 19 infection in a 65 year old male. The conjunctival swab did not reveal any bacterial or fungal infection. The conjunctivitis resolved in two weeks with lubricants and preservative free moxifloxacin eye drops. The authors also concluded that virus shedding in the conjunctiva may persist even after the nasopharyngeal swab becomes negative for SAR CoV virus [16] [Fig 3 see Color pages section]

B. Viral keratoconjunctivitis

Keratoconjunctivitis as the initial presentation in a patient with mild respiratory symptoms has been reported by Cheema et al. The patient presented with redness, discharge, and photophobia and was treated as herpetic keratoconjunctivitis, and later, as epidemic keratoconjunctivitis with oral valacyclovir and topical moxifloxacin. SARS CoV 2 testing turned out to be positive. This case highlights the importance of considering conjunctivitis as a presenting symptom of COVID 19 [17]

In a case report from China, Guo et al. reported a patient with moderate severe COVID 19 infection with left eye conjunctivitis developing ten days after onset of COVID-19 symptoms and conjunctival swab was positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR). It was treated with topical levofloxacin and lubricant and resolved attributing this to local invasion and inflammation of ocular surface caused by virus. After five days the patient presented with a relapse and peripheral corneal staining. The conjunctival

swab was negative for SARS-CoV-2 and HSV but interleukin-6 (IL-6) level was raised and patient responded to a course of topical steroids supporting the relapse to be due to a cytokine surge caused by autoimmune response mediated by the virus. A longer follow up with proper use of topical glucocorticoid is recommended by some to diminish the risk of immune mediated keratoconjunctivitis[18].

C. **Haemorrhagic and pseudomembranous keratoconjunctivitis**

Navel et al. in France reported a case of a 63 year old male patient with severe COVID 19 infection, admitted in intensive care unit (ICU), developing hemorrhagic and pseudomembranous conjunctivitis 19 days after the onset of systemic symptoms. Treatment was with azithromycin and dexamethasone drops and daily debridement of the pseudomembrane [19].

D. **Conjunctivitis in children**

A 30 fold increase in the incidence of Kawasaki disease like condition has been reported in children in some parts of Italy with strong association with COVID 19. This atypical presentation is known as multisystem inflammatory syndrome in children (MIS C).[20] Kawasaki disease, a form of self limiting vasculitis, is associated with iridocyclitis, punctate keratitis, vitreous opacities, papilloedema, subconjunctival haemorrhage and conjunctival injection.[21] In the literature available on MIS C, the ophthalmic manifestations have mainly been in the form of conjunctivitis. MIS C is commonly being noted to have serological positivity for SARS CoV 2 than on nasopharyngeal swab indicating it to be a manifestation of delayed immunological response to COVID 19. Treatment is directed towards suppressing the systemic inflammation. Corticosteroids, intravenous immunoglobulin (IVIG) and aspirin have been used in the cases reported [20].

E. **Episcleritis**

A case of episcleritis as the initial manifestation of COVID 19 has been described in a 29 year old male by Otaif et al. Patient had history of foreign body sensation in the left eye and examination revealed nasal conjunctival and episcleral congestion with blanching with phenylephrine. He developed mild viral infection with symptoms appearing three days after the ocular signs [22]. Managna et al. reported another case of episcleritis which developed seven days after the onset of symptoms of COVID 19 infection. Most cases of episcleritis are idiopathic and self limiting. About a third of them may be associated with viral infections including ebola, HSV and hepatitis C and now possibly, SARS CoV 2 virus [23].

F. **Eyelid manifestations**

Eyelid manifestations in the form of meibomian orifice abnormalities and lid margin hyperemia/telangiectasia was found in 11/27 (38%) patients in the study by Meduri et al in Italy. Blepharitis positively correlated with the COVID-19 disease duration.[24] It may develop as late manifestation of the disease and the incidence is also expected to rise in the post pandemic era especially in patients with pre existing ocular surface alteration.

Posterior segment manifestations

Posterior segment involvement has varied manifestation and are actually vascular, inflammatory, and neuronal changes triggered by the viral infection but not specific to COVID 19. The median duration between appearance of ophthalmic symptoms and the COVID 19 symptoms /diagnosis was 12 (17.6 ± 13.1 , 4–55) days.

Retinal vascular occlusions

1. Central retinal vein occlusion (CRVO)

Patients of COVID 19 are in a procoagulant state evident by elevated D dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and

cytokines even in the absence of common systemic conditions like hypertension, diabetes or dyslipidemia. Additionally, intermittent hypoxia in patients with pneumonia can induce the endothelial cells to release tissue factor and trigger the extrinsic coagulation cascade. In the impending stage, high dose steroids may help to normalize the inflammatory markers and coagulation indices. Management is with anti-vascular endothelial growth factor (anti-VEGF) in the established phase. [25- 28] In patients with systemic comorbidities with severe COVID 19 infection, early anticoagulant prophylaxis should be considered. [Fig 4(a) and (b) see Color pages section]

2. Central retinal artery occlusion (CRAO)

The reported cases of Central retinal artery occlusion, had elevated inflammatory markers including IL-6, CRP, ferritin, fibrinogen and D dimer as a result of severe COVID 19 infection, possibly resulting in the vascular occlusion [29,30] In the case reported by Dumitrascu et al., incomplete ophthalmic artery occlusion developed despite the patient being on enoxaparin for deep vein thrombosis[30]. Walinjkar JA et al, reported a case of combined CRAO+CRVO in 66 year old male patient with no significant past medical systemic history but had a positive COVID-19 disease [31]

3. Acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy (PAMM)

AMN is a rare condition with unknown etiology but, about 50% have been shown to be associated with respiratory or influenza like illness. Ischemic mechanism involving the deep capillary plexus has been proposed. Cases of AMN and PAMM have been reported following/concurrently with COVID 19 diagnosis [32-34]. Goyal et al, reported a 32-year-old man who presented with 3-day onset of paracentral and triangular negative scotoma in RE infero-temporal visual field. He had recovered from COVID-19 infection 4 months prior.

Based on the characteristic symptoms, the fundus lesions and OCT findings he was diagnosed as post COVID-19 RE symptomatic AMN, and bilateral asymptomatic PAMM. He was placed under observation [35]

Retina

1. Vitritis and outer retinal abnormalities

The presenting complaint in this case was bilateral redness in eyes. SD OCT showed hyperreflectivity at the level of posterior vitreous hyaloid corresponding to the vitritis. Other infectious causes of vitritis like HSV, cytomegalovirus (CMV), syphilis, bartonella, toxoplasma, borrelia, toxocara, and inflammatory diseases were ruled out and COVID 19 was presumed to have led to the development of abnormalities detected on OCT [36].

2. Acute retinal necrosis (ARN)

The reported patient was immunocompromised with relapsed diffuse large B cell lymphoma and had completed chemotherapy two months ago. A known case of systemic lupus erythematosus (SLE), she presented with ocular complaints of floaters and reduced vision. Intravitreal specimen tested positive for varicella zoster virus (VZV) but not for COVID19.[37] ARN is not common in immunosuppressed states, neither is the amount of inflammation seen in this patient which led to the presumption that COVID 19 had a role to play in triggering the VZV related ARN by its effect on the immune system. It is possible that SARS CoV 2 may compromise the blood retinal barrier allowing a heightened inflammatory response.

3. Intraocular infections

Goyal M et al reported three cases of intraocular infection in COVID-19 patients, one being a suspected fungal endophthalmitis in a COVID-19 recovered patient who developed steroid induced diabetes and ocular complaints after completing a course of steroids to treat

COVID-19 infection. The patient responded well to intravitreal and systemic antifungals. The second case was diagnosed as Candida retinitis in a patient (diabetic and hypertensive) who was hospitalized for severe Candida septicemia, with renal infection during COVID-19 infection. The patient responded to intravitreal and systemic antifungals. They postulated that these infections could be as a result of immunosuppression caused by COVID-19 infection, and the steroids used for its management. It is recommended that surveillance for systemic fungal infections should be done in severe COVID-19 infection [38, 39]. They also reported a case of choroidal abscess due to tuberculosis, in association with recent COVID-19 [35].

4. Other manifestations

There are reports of peripheral retinal haemorrhages, macular hyperpigmentation, retinal sectoral pallor, peripapillary flame shaped hemorrhages, hard exudates, and cotton wool spots in severe COVID-19 patients [40]. Goyal M et al reported a case of prefoveal haemorrhage secondary to thrombocytopenia in systemic Pseudomonas sepsis. Sepsis and signs of multi-organ injury typical of sepsis occur in approximately 2-5% of those with COVID-19[41].

5. Treatment related retinal complications

Central serous chorioretinopathy [Fig 5(a) and (b) see Color pages section] secondary to steroid used to treat COVID-19 patients and Voriconazole induced transient visual disturbances in a patient of invasive systemic aspergillosis along with COVID-19 infection were also reported [35]

Uvea

Serpiginous choroiditis

Reactivation of serpiginous choroiditis following COVID 19 infection was reported by Providencia et al [42]. There are unpublished cases of multifocal or serpiginous choroiditis presenting in patients with a history of SARS CoV 2 infection. It is difficult to determine whether these are new onset or

reactivation of inflammation. Autoimmunity activated by SARS CoV 2 is believed to play a role in this. Tests for tuberculosis (TB), Hepatitis B and C (HBV, HCV), human immunodeficiency virus (HIV), borrelia, and syphilis should be done to diagnose serpiginous like choroiditis and before starting immunomodulatory therapy [42].

Neuro-ophthalmic manifestations of COVID-19

The neuro-ophthalmic manifestations of COVID-19 are mostly related to demyelinating disease. While the mechanism of these manifestations are still unknown, hypotheses include direct neuronal invasion, endothelial cell dysfunction leading to ischaemia and coagulopathy, or a widespread inflammatory "cytokine storm" induced by the virus [43]. The median gap from COVID 19 to development of ophthalmic symptoms was 5 (mean 11.3 ± 13.3 , 0-42) days.

1. Papillophlebitis

Papillophlebitis is an uncommon condition seen in healthy, young adults and one such case has been reported in a COVID 19 patient. There is painless, unilateral, slight diminution of vision with enlarged blind spot on visual fields. Ophthalmic findings include dilated tortuous retinal vessels, disc edema, superficial retinal hemorrhages, cotton wool spots with or without macular edema. While the final visual prognosis is quite favorable, about 30% of the cases develop vision threatening ischemic venous occlusion with consequent neovascular glaucoma and macular oedema. Systemic evaluation for hypercoagulable state, vasculitis syndromes, hyperviscosity, and vascular inflammatory disorders should be done to determine the possible etiology that could result in inflammation of retinal vasculature and capillaries of the disc. The role of COVID 19 as a possible cause comes in view of its association with coagulopathy and disproportionate inflammatory response or cytokine storm. [44]

2. Optic neuritis

The SARS CoV 2 virus has been shown to

cause optic neuritis in animal models. Neurotropism of the virus has been proposed as one of the mechanisms for the neurological and neuro ophthalmic manifestations. The reported cases had anti myelin oligodendrocyte glycoprotein (MOG) antibodies. Cerebrospinal fluid (CSF) examination, immunological profile, viral panel and MRI brain did not reveal any other underlying etiology. Treatment with intravenous methylprednisolone (IVMP) followed by oral prednisolone led to visual recovery and resolution of disc edema. MOG antibody associated optic neuritis in the setting of COVID 19 is a parainfectious demyelinating syndrome with a viral prodrome. The virus has not been isolated from the CSF of the patients indicating that the virus may not be directly involved, rather it maybe an immune mediated insult [45, 46]

3. Adie's tonic pupil

Adie's tonic pupil can result from systemic conditions like diabetes or other viral infections. The reported case was a health care worker who gave a history of retro ocular pain and reading difficulty two days after the onset of systemic COVID 19 symptoms. Pupillary hypersensitivity to 0.1% pilocarpine confirmed the diagnosis. The patient also had bilateral chorioretinopathy. Systemic oral steroids led to full anatomical and functional recovery, further favoring the role of autoimmune factors mediated by COVID 19 in the development of both chorioretinopathy and Adie's tonic pupil [47].

4. Miller Fisher Syndrome (MFS) and cranial nerve palsy

MFS with acute onset ataxia, loss of tendon reflexes, and ophthalmoplegia and cases of cranial nerve palsies have been reported in several patients recently diagnosed with COVID 19 [48-53]. Patients give history of acute onset of diplopia as the ocular complaint. 6th nerve [Fig 6 see Color pages section] was the most commonly involved

followed by oculomotor nerve. A case of right sided facial nerve palsy has also been reported [53]. RT PCR was positive for SARS CoV 2 but not for HSV and VZV. Cases of MFS responded well to intravenous immunoglobulin (IVIG) while cranial nerve palsies resolved spontaneously in most cases in 2-6 weeks. In these cases, again a misdirected immune system triggered by the viral infection is believed to be at fault

5. Neurogenic ptosis

Acute onset of bilateral ptosis with other neurological signs of Guillain-Barre syndrome (GBS) was reported by Assini et al. from Italy [54]. Symptoms developed almost 20 days after severe COVID 19 infection. No SARS CoV 2 virus was detected in the CSF. GBS with cranial nerve involvement can thus be a late manifestation of severe COVID 19 infection. Good response to immunoglobulin supports the immune mediated pathogenesis.

Delayed onset of ocular myasthenia gravis was reported by Huber et al. in a 21 year old healthy woman [55]. Her antibody titers were suggestive of past infection with SARS CoV 2. Acetylcholine receptor antibodies were positive. She was treated with IVIG with gradually increasing dose of pyridostigmine. It is likely that COVID 19 infection can potentially trigger or exacerbate autoimmune diseases.

6. Cerebrovascular accident (CVA) with vision loss

Acute vision loss following CVA can also result from the procoagulant state in COVID 19 infection. Pre-existing endothelial dysfunction may make patients more susceptible. Acute onset of bilateral, painless vision loss should prompt the treating physicians to advise an urgent imaging of the brain with angiography [56]. Yang et al. described the development of bilateral supranuclear gaze palsy with right branch retinal artery occlusion in a 60 year old patient with an infarct in left paramedian

midbrain [57].

Orbital manifestations of COVID-19

The median time of presentation of orbital symptoms from the development of COVID-19 symptoms was 12 days and majority were seen in moderate to severe COVID-19 disease.

1. Dacryoadenitis

It presents as a painful lacrimal gland mass and the most common cause is viral infection hence the association with COVID-19 infection. The reported case of acute dacryoadenitis was described as a late complication of SARS-CoV-2 virus infection [58]. In early stages of disease, the virus can travel to the lacrimal glands via the lacrimal ductules or by direct hematogenous spread. Later, immunological response incited by the virus may affect the lacrimal gland producing inflammation. It responds well to systemic steroids [Fig 7 see Color pages section]

2. Retro-orbital pain

Bilateral retro-orbital pain was a prominent symptom and can sometimes be the presenting symptom of COVID-19 disease as reported by Ruiy W et al., mimicking conditions like dengue [59]

3. Orbital cellulitis and sinusitis

There are reported cases of orbital cellulitis in COVID-19 patients where the suggested mechanism is that the COVID-19 induced upper respiratory congestion can compromise muco-ciliary clearance with secondary sinus obstruction and bacterial infection. The superior ophthalmic vein thrombosis in a reported case with facial vein extension may be a thrombotic complication of SARS CoV 2[60].

4. Mucormycosis

Mucormycosis is a life threatening, opportunistic infection and patients with moderate to severe COVID 19 are more susceptible to it because of the compromised immune system with decreased CD4+ and

CD8+ lymphocytes, associated comorbidities such as diabetes mellitus which potentiates both the conditions, decompensated pulmonary functions, and the use of immunosuppressive therapy (corticosteroids) for the management. Literature shows that rhino orbital-cerebral (ROC) mucormycosis can present concurrently with COVID 19 infection in patients under treatment or diagnosed on preoperative evaluation [61-63]. Mortality rate is as high as 50% even with treatment.

Symptoms of rhino orbital mucormycosis developed as late as 30-42 days after the diagnosis of COVID 19 [64]. High index of suspicion, early diagnosis with histopathological and microbiological evidence, appropriate management with antifungals (intravenous liposomal amphotericin B) and aggressive surgical debridement (functional endoscopic sinus surgery and orbital exenteration) can improve survival [Fig 8 see Color pages section]

5. Orbital histiocytic lesion

There is a single (unpublished) report of a probable Rosai-Dorfman disease or a benign histiocytic proliferative lesion in the orbit seen six months after COVID-19 infection in an elderly patient. The infection with SARS-CoV-2 may have had a role in this with its influence on the immune system of the body [65]

Treatment related ocular manifestations

The medications that have been used to treat COVID-19 also have ocular toxicities. Long term use of chloroquine and hydroxychloroquine can lead to retinal toxicity but it is not expected or seen with the brief period of use for COVID 19. Lopinavir/Ritonavir may cause reactivation of autoimmune conditions. Ribavirin has not been used much for COVID 19 but is known to cause retinopathy, retinal vein occlusion, serous retinal detachment, non-arteritic ischemic optic neuropathy and Vogt Koyanagi Harada (VKH) disease. Interferon has been associated with retinopathy, VKH, conjunctivitis, uveitis, optic neuropathy, corneal ulcers, epithelial defects and Sjogren's syndrome. Tocilizumab has

been reported to produce cotton wool spots and retinal hemorrhages. Systemic corticosteroids are known to cause cataract, glaucoma and central serous chorioretinopathy. The risk of life threatening fungal infection in predisposed individuals cannot be overemphasized. Central retinal vein occlusion has been reported in patients receiving IVIG. These points should be kept in mind by an ophthalmologist during the history and examination of patients [66]

COVID-19 vaccine related complications

The COVID-19 vaccination has come as a ray of hope to the ailing world but the scattered reports of ocular adverse effects of the inactivated vaccines are also pouring in. Pichi F et al. in their case series including 9 eyes of 7 patients showed that patients developed transient ocular adverse events 5.2 days after COVID vaccination (Sinopharm) with varied manifestations like anterior scleritis, episcleritis, acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy (PAMM) and central serous chorioretinopathy (CSCR). The theoretic pathogenesis of inactivated COVID-19 associated ocular inflammation is not known. Commonly proposed mechanisms include molecular mimicry and antigen-specific cell and antibody mediated hypersensitivity reaction [67]

The storm of COVID-19 that has gripped the world is far from over. As ophthalmologists are at high risk while examining patients at close quarters all the necessary precautions like room cleaning, hand washing, wearing of protective gear by providers and masks by patients, using slit-lamp/indirect ophthalmoscopy shields, triaging patients, proper history of exposure and social distancing are to be followed strictly to curb the spread of this disease.

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Surgical Issues in COVID-19: Maintenance of safety and regulation in surgical care, the effect on patients, education, career and research and the role of surgery in COVID care



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INTRODUCTION

In December 2019, a novel coronavirus was identified as the cause of many pneumonia cases in Wuhan, China. The new virus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to the outbreak of coronavirus disease 2019 (COVID 19)¹ and eventually a global pandemic was declared on 11th March 2020. Due to its rapid global spread, healthcare systems and their workers worldwide faced tremendous challenges, and India was no exception. Surgery is a basic pillar of medical care and as such, the surgical workforce has faced distinct challenges compared with nonsurgical specialties during this pandemic. Now one and a half years into this pandemic it is time to review what we have learned.

This article attempts to discuss the specific issues faced by the surgical community under the following three broad categories:

- Evolving safety protocols and the regulation of delivery of surgical care
- The detrimental effects on patients with surgical disease, healthcare systems and surgical education, research and career development, and
- COVID-specific surgical situations

Evolving safety protocols

During the initial stages and periods of maximum intensity of the pandemic, guidelines issued by government agencies and those such as the centre for disease control and prevention, called for the delay of all elective procedures². These recommendations were made with the foresight of anticipated infrastructure and staff shortages. However, as the pandemic progressed, it became apparent that not only was there an increasing

number of COVID positive emergency cases presenting for surgical intervention but also that it was inevitable to restart elective surgical procedures at some point of time.

There is a well-documented increased likelihood of contracting COVID 19 in hospital with reports of thousands of healthcare professionals contracting the infection despite adherence to infection control measures³. This also led to the realization that first and foremost, to deliver surgical care, a healthy and functional surgical workforce is required. Studies have also shown an increased mortality rate in patients who underwent elective surgeries during the incubation period of COVID 19, up to 20.5% in some series⁴. This could be explained by the lowering of cell-mediated immunity after surgery, which is vital for combating viral infections⁵.

The rationale behind knowing the COVID-19 status of any surgical candidate is ensuring patient safety, reduction of postoperative complications and potential transmission of the novel coronavirus from an unknown carrier to medical staff or to other patients. While spreading the virus in the operation room and during hospital stay is potentially managed by personal protective equipment, the complications that may present during patient's recovery are not under our control⁶. Though the data were retrieved from a small available number of publications, this morbidity and mortality risk is unacceptable and could be minimized or even avoided primarily by the preoperative diagnosis of patient's COVID-19 status⁷.

With that said, like all screening tests, a true benefit from preoperative screening depends on COVID-19 local prevalence rates and the availability of an accurate objective test. Screening is of extra importance in situations that may lead to different clinical management approaches for the patients and staff. RT-PCR COVID-19 testing was shown to have

high specificity with moderate sensitivity, resulting in cases of false negative results. Usually, these false results are a consequence of incorrect sampling and could be addressed by education of health care staff^{8,9}. Today and especially in the near future, when isolation and quarantine measures ease up, and expecting the comeback of elective surgeries, knowing the preoperative COVID-19 status will be of great clinical importance. The preoperative diagnosis will lead health care providers to use the right protocols aiming to reduce postoperative complications and fatal morbidity. Most importantly, a known COVID-19 status will improve the medical staff decision making concerning the use of protective equipment aiming to prevent the hazardous staff infection¹⁰.

To streamline decision making and the widespread use of precautions international and national bodies such as the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the European Association for Endoscopic Surgeons (EAES)¹¹ and the Association of Surgeons of India (ASI)¹² have come up with detailed guidelines on surgical strategies in relation to the COVID 19 crisis. The Ministry of Health and Family Welfare (MoHFW)^{13,14} of India has also brought out sets of standard operating procedures and guidelines on the appropriate use of personal protective equipment (PPE) and steps for the prevention of COVID 19 in non-COVID areas and hospitals.

To summarize the takeaway points from these guidelines:

- Setting appropriate use of PPE. This could include triple layer surgical masks in low risk environments to fit-tested particulate respirators (like N95 masks), long-sleeved gowns and eye-protection and latex disposable gloves in aerosol generating procedures.
- Scheduling of out-patient appointments in a way to maintain social distancing and minimizing the number of attenders accompanying the patient. Recourse to tele-medicine as much as possible.
- Guidelines for prioritization of elective surgeries were put in place to conserve essential resources and to restrict the risk of

transmission among patients and staff. It was recognized that emergency surgeries that could not wait for up to 12 hours for results of a COVID 19 RT-PCR test, should go ahead regardless, taking necessary precautions to isolate the patient and safeguard all medical personnel in close contact. It was recommended that each institution set up a surgical review committee comprised of surgeons, anesthesiologists and nursing personnel to adjust the prioritization process with the local, regional and national circumstances. Though elective surgeries were recommended to be commenced once the COVID 19 curve shows a continuous decline for fifteen days, it was also recommended that surgeons follow local, state and MoHFW recommendations in this regard.

- **Surgery during the pandemic can be divided into 5 categories:**
 - Emergency surgery, to be taken up within an hour (e.g.: trauma with active bleeding, life-threatening traumatic hemoperitoneum with hemodynamic instability, bowel gangrene, ruptured aortic aneurysm)
 - Urgent surgery, within 24 hours (e.g.: Bowel obstruction, perforation of hollow viscous, unresolved obstruction, complicated appendicitis, and complicated cholecystitis, acute limb ischemia, amputation for wet gangrene)
 - Urgent elective surgery, within 2 weeks (e.g.: colorectal cancer with local complications, symptomatic carotid stenosis, irreducible inguinal hernia without signs of obstruction, amputation for dry gangrene)
 - Elective essential surgery, 1-3 months (e.g.: colorectal liver metastases, symptomatic chest or stomach, hernias with recurrent incarceration symptoms, conservative therapy refractory symptomatic anal fissure)
 - Elective surgery, discretionary/ 3 months (e.g.: plastic-aesthetic procedures, ostomy relocation without local complications, functional rectal diseases)

The first 2 categories need to be taken up even without a COVID report being available.

- Recommendations were made on adapting surgical techniques to reduce viral exposure. Although previous research has shown that laparoscopy can lead to aerosolization of blood borne viruses, there is no evidence to indicate that this effect is seen with COVID-19, nor that it would be isolated to minimally invasive surgical (MIS)procedures. Nevertheless, erring on the side of safety would warrant treating the coronavirus as exhibiting similar aerosolization properties. For MIS procedures, use of devices to filter released CO₂ for aerosolized particles should be strongly considered. Proven benefits of MIS of reduced length of stay and complications should be strongly considered in these patients, in addition to the potential for ultrafiltration of the majority of aerosolized particles. Filtration of aerosolized particles may be more difficult during open surgery. Electrosurgery units should be set to the lowest possible settings for the desired effect. Use of monopolar electrosurgery, ultrasonic dissectors, and advanced bipolar devices should be minimized, as these can lead to particle aerosolization, and if available, monopolar diathermy pencils with attached smoke evacuators should be used¹⁵.
- Guidelines pertaining to where surgical patients should be operated upon and cared for recommend the establishment of separate COVID and non-COVID emergency rooms, the establishment of a separate COVID operating area and surgical non-intensive care ward. In our hospital, in cooperation with the hospital infection control team and facility management, a non-intensive care ward was repurposed and newly set up. This included the establishment of 3 discrete areas: COVID positive area (infectious area), COVID suspicious area (potentially infectious area) and non-infectious area.

A relatively isolated theatre with separate access and a negative pressure environment should be designated for surgery on COVID patients. The negative pressure method is

restricted in the anteroom and the induction room. The scrub area and the main operating room have positive pressures. The main operating room should have more than 25 air exchange cycles per hour. Operating rooms are usually designed to have positive pressure to prevent intraoperative contamination. Coronavirus is 125 nm in diameter and a high proportion of particles (up to 100%) are captured by high-efficiency particulate air (HEPA) filters. This may be combined with the aforementioned high-frequency air exchanges to reduce the chance of virus dissemination¹⁶.

- Informed consent for surgery, which is a critical component of surgical practice, has become a challenging issue in the time of COVID 19 infection. The true impact of asymptomatic or pre-symptomatic COVID 19 disease on physiologic risks of surgery and/or anaesthesia is not yet understood. The risk of nosocomial COVID 19 acquisition for a patient coming to the hospital, nor the risk of transmission of COVID 19 from unsuspectedly infected patients to the operative team members is known. It is important to recognize the scientific, ethical, and moral uncertainties that surround the patient care during this pandemic and how they might be reflected in informed consent discussions. COVID 19 has added an additional imperative to the informed consent process, transparency about potential but unknown risks and an honest admission of how little we currently understand about the surgical outcomes of COVID 19 positive patients and patients with unknown COVID 19 status¹⁷.

Repercussions of COVID 19 on patients, the healthcare system and surgical education, research and career advancement

The immense suffering of COVID-19 patients, especially during the infamous second wave in India, is widely known. What has been bore subtle are the detrimental effects of the pandemic on surgical patients. Many patients with surgical diseases have avoided care because of concerns of acquiring COVID-19 at hospitals or in clinician's offices. Non-urgent and non-emergency care has been delayed

and has created a large backlog of patients who require surgical care. The effects on patients with cancer or chronic debilitating disease and patients awaiting organ transplant have yet to be defined.

The financial implications of the surgical shutdown have been far-reaching. Many health care employees have been affected by pay cuts, furloughs, and layoffs. Surgical private practices that could not bear the financial challenges of the pandemic have been forced to shut down. Some surgeons have retired early or decided to leave the surgical profession¹⁸. Costs get escalated with use of PPE for all involved in surgery and postoperative care. It is estimated to be over ¹ Rs. 15,000 per case. Agencies like ESI/CGHS/ECHS and even insurance need to be informed and directed through the MoHFW to exclude the cost from the package for operations agreed upon¹². All of these problems further influence the surgical workforce in a time during which there is likely a greater need for surgical care. Trainees who planned to pursue further specialist training overseas have encountered additional challenges with obtaining visas further hindering their surgical careers.

The COVID-19 pandemic has also created challenges in the education of the future surgical workforce. During the initial phases of the pandemic, when PPE shortages were common, most medical students were removed from clinical care rotations. With the shutdown of non-urgent, nonemergency surgery, residents were no longer gaining experience in the operating room and clinic. Furthermore and especially during the peak of the pandemic, when many of our colleagues from medical specialties were under tremendous strain and surgical professionals were allowed to carry out only the most urgent surgeries, many surgical trainees and faculty were diverted towards COVID duties to decrease the load from their medical brethren. The implications for this are far-reaching. Regarding the medical students, their exposure to surgery is now limited. Fewer medical students may choose careers in surgery due to limited exposure. For those medical students who wanted to pursue surgery, concern related to the close patient-physician contact needed for surgery may lead them to choose a different profession. For those medical students still pursuing surgery, there may be confusion and anxiety over deciding which surgical residency

program they should apply to because they could not participate in the different rotations they had planned. Graduating surgical trainees who haven't been able to meet the appropriate case load requirement might not be fully prepared to enter independent surgical practice and are at risk for stigmatization as the "COVID batch".

Just as the pandemic has affected clinical care, it has also affected research and career development. All research, including clinical trials (barring those involved with vaccines for COVID-19), has slowed or stopped. The ultimate effect of this shutdown on new scientific discovery and innovation is not clear. There is also a need to recognise the increased strain on healthcare providers with children especially as many schools continue with virtual education. An analysis of manuscripts submitted to JAMA Surgery revealed a proportional decrease in submissions from female authors during April and May 2020 compared with April and May 2019¹⁹. This reflects the disparity that already exists between male and female healthcare providers with children, with female parents shouldering more of the home and childcare responsibilities than their male counterparts. It will be imperative for academic institutions to recognize this differential career influence with respect to promotion and tenure in the future. There is also a great need to put processes in place that will allow all clinicians with children to navigate the challenges associated with delivering care during this pandemic.

Surgery for COVID related complications

While COVID has posed unseen challenges to the entire surgical fraternity, vascular and ENT surgeons have developed a unique perspective while treating conditions like thromboembolism and rhino-orbito-cerebral mucormycosis (ROCM).

The role of the vascular surgeon

Thrombotic complications in patients with coronavirus disease 2019 (COVID-19) present in a variety of ways, most commonly with venous thromboembolism, but also with ischemic complications related to thrombosis of extremity, cerebral, coronary, and visceral arteries. Early recognition of acute limb ischemia (ALI), which is a sudden decrease in the perfusion to an extremity, and intervention, when possible, can help reduce

mortality in these very ill patients and maximize the chance for limb salvage.

The data available on the incidence and characteristics of arterial thromboembolic complications in patients with COVID-19 come from a handful of case series and individual case reports. The incidence of ALI associated with patients with COVID-19 who require hospitalization ranges from 3 to 15 percent²⁰. Based on several case series²¹, patients with COVID-19 associated ALI were, on average, over 60 years of age with body mass index >25 and had typical cardiovascular risk factors including hypertension, PAD, and diabetes²², however, it is important to note that COVID-19 associated ALI can occur in young, otherwise healthy individuals. COVID-19 associated ALI has occurred in patients receiving thromboprophylaxis²³.

The classic clinical features of ALI (Figure 1 see Color pages section) include the 6 Ps (pain, pallor, poikilothermia, pulselessness, paresthesia, and paralysis). The degree of sensorimotor deficits and Doppler findings determine the severity of ALI and the severity of ALI determines the urgency and type of diagnostic evaluation and course of treatment. Infected patients with minimal or no symptoms of COVID-19 can develop a prothrombotic state and ALI has also been described following recovery from a mild cases of COVID-19²⁴. Thrombosis of prior vascular reconstruction including stents and bypass grafts have also been reported.

Based on the patient's overall stability, degree of ischemia, and limb viability, a determination needs to be made whether intervention is appropriate. Because of the severe pulmonary complications associated with COVID-19, critically ill patients may not be candidates for revascularization. Similar to damage control in trauma patients, the principle of "life over limb" is justified. Options for revascularization include open thrombectomy (with use of adjuncts like endarterectomy, patch angioplasty and bypasses), catheter-directed thrombolysis or percutaneous mechanical thrombectomy or, at times, a hybrid combination of both open and endovascular techniques.

In our experience at this institution, COVID related limb ischemia was more often seen after the period of maximum infectivity and in the post-COVID

period (4 weeks after the onset of infection). There was the added complication of late presentation with advanced ischemia either due to the restriction of movement hindering access to advanced medical care at tertiary referral centers such as ours and also patient apprehension. In those presenting with thromboembolic sequelae, we were often but not always able to identify aortic mural thrombi as the source (Figure 2 see Color pages section). As has been reported in literature COVID-related thrombosis was also seen complicating prior vascular reconstructions including arteriovenous fistulas for dialysis access. Our approach to DVT in COVID patients was mostly with anticoagulation, as is the norm, though one particular case which presented with venous gangrene (Figure 3 see Color pages section) due to extensive ilio-femoral venous thrombosis in a patient with acute COVID-19 with mild respiratory symptoms. Apart from severe swelling of the entire limb, there was blackish discoloration of the foot with fixed mottling and blebs seen in the leg. Triphasic Doppler arterial flow was heard till the ankle and her ankle brachial pressure index (ABPI) was normal. She was anticoagulated and an emergency fasciotomy was done, following which she needed an above knee amputation after demarcation of the gangrene.

The ENT perspective

The challenges for the ENT specialist started in the outpatient department itself. The ENT fraternity was cautioned about the risks of examining the upper respiratory tract. Many of our colleagues devised different concepts and innovative technique to examine and treat the ailing patients. This was followed by the need to establish and maintain an alternative airway in COVID-19 positive patient²⁵. Tracheostomy being a high aerosol-generating procedure, it posed doubts, especially with regard to the indications, surgical aspects and risks to healthcare workers. Data related to the indications, outcome and safety of the team performing tracheostomy were limited. The ideal time to perform a tracheostomy in a COVID-19 patient was debated, with many regulatory bodies cautioning the ENT specialist in performing the procedure²⁶. Our team started performing tracheostomies as early as in May 2020 taking adequate precautions to protect oneself and also other members of the team. Hence new protocols

were adapted based on patient needs.

An institutional protocol for performing tracheostomies was drafted and all healthcare workers who volunteered to help were sensitised to the precautions and the risk to self and patients. Informed high risk consent was obtained from the patient-attenders and the procedure was performed. Modifications in the routine procedure of tracheostomy were made: once the neck was incised, strap muscles separated, trachea exposed and complete haemostasis achieved, the anaesthetist / intensivist was asked to stop ventilating for 30 seconds following which a rapid sequence of opening the trachea and inserting a double lumen cuffed tracheostomy was performed which reduced the chances of aerosol generation. The double lumen helped in maintaining the airway during the immediate post-operative care and also later for de-cannulation. A total of about 80 Covid 19 Tracheostomies were performed. Presently we recommend early tracheostomies to help decrease the requirement of sedation and control of airway and bronchopulmonary toileting with the help of a dedicated team. High level personal protection equipment (PPEs) are to be used while performing the procedure. In order to minimise aerosol exposure, the number of assistants and total time for the surgery should be reduced.

Next, it was during the second wave of COVID -19 that our country faced another crisis. This time it was in the form of an invasive fungal infection – mucormycosis, or the black fungus as it is commonly referred to, which complicated the management of COVID-19. Mucormycosis, also known as rhino-orbito-cerebral mucormycosis (ROCM), reached epidemic proportions and the shortage of amphotericin posed additional problems²⁷. The entire ENT fraternity along with their team of allied specialities - General Physicians, Endocrinologists , Neurosurgeons and Ophthalmologist (Figures 4-6 see Color pages section) rose up to meet the situation. A combined team effort to operate on the nose and paranasal sinus of the COVID-19 patient again posed the challenges of aerosol generation.

Timely identification, diagnosis and intervention were the key to better outcomes. Diagnostic nasal endoscopy with tissue biopsy sent for 10% KOH

mount and MRI with contrast of the nose and paranasal sinuses were crucial for diagnosis²⁸. Once the diagnosis was established, immediate endoscopic debridement of the nose and paranasal sinus was followed by antimicrobial therapy was initiated. All our patients underwent an endoscopic debridement of the nose and paranasal sinuses. The debridement was confined to the sinuses and the adjacent structures involved. More extensive surgeries were performed by trans-oral endoscopic assisted debridement of the involved bone and soft tissues. Neurosurgical help was sought in cases of intracranial involvement who used the bifronto-osteoplastic flap to remove the intracranial disease and then a combined clearance of the skull-base disease was given by the neurosurgical team approaching from above and the ENT team approaching the disease from below. Radical debridement with an external approach was avoided in all patients. The Prosthodontics team then helped in minimizing disfigurement by creating artificial dentures and orbital prostheses.

Conclusion

In conclusion, surgical disciplines have faced substantial challenges during the COVID-19 pandemic, and the effects on the surgical profession will be lasting. The long-term effects on patients with surgical disease have yet to be fully realized; however, it is clear that operating on patients with COVID-19 is associated with a significantly increased odds of morbidity and mortality. The surgical workforce will be strained by further shortages. Medical student education and surgical resident experience have changed. Health care systems are facing unprecedented financial challenges. The effect on research and clinical trials may be significant. Although the future is uncertain, and it is not possible to predict how long this pandemic will last, hospitals and surgeons should not expect to return to the pre-pandemic approaches for the delivery of surgical care. Many of the changes that have been instituted during the COVID-19 pandemic are the new reality, and the surgical community must learn to evolve with and accept these changes. The future of the profession depends on it.

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Coronavirus disease 2019 (COVID-19) is a respiratory infection caused by SARS-CoV-2 (COVID-19 virus). The COVID-19 virus is transmitted mainly through close physical contact and respiratory droplets, while airborne transmission is possible during aerosol generating medical procedures like Nebulization , open suctioning , Intubation and Positive pressure non invasive ventilation etc .

Environmental surfaces in health-care settings include furniture and other fixed items inside and outside of patient rooms and bathrooms, such as tables, chairs, walls, light switches and computer peripherals, electronic equipment, sinks, toilets as well as the surfaces of non-critical medical equipment, such as blood pressure cuffs, stethoscopes, wheelchairs and incubators.

Environmental surfaces are more likely to be contaminated with the COVID-19 virus in health-care settings where certain medical procedures are performed which are mentioned above.

In all settings, including those where cleaning and disinfection are not possible on a regular basis due to resource limitations, frequent hand washing and avoiding touching the face should be the primary prevention approaches to reduce any potential transmission associated with surface contamination.

Like other coronaviruses, SARS-CoV-2 is an enveloped virus with a fragile outer lipid envelope that makes it more susceptible to disinfectants compared to non-enveloped viruses such as rotavirus, norovirus and poliovirus.

One study found that the COVID-19 virus remained viable up to 1 day on cloth and wood, up to 2 days on glass, 4 days on stainless steel and plastic, and up to 7 days on the outer layer of a medical mask

Another study found that the COVID-19 virus survived 4 hours on copper, 24 hours on cardboard and up to 72 hours on plastic and stainless steel

Principles of environmental cleaning and disinfection

Always remember 4 Ds

1. Disinfection selection
2. Duration of contact time
3. Dilution as per the manufacturers recommendation
4. Detoxification of the used disinfectant

Cleaning helps to remove pathogens or significantly reduce their load on contaminated surfaces and is an essential first step in any disinfection process. Cleaning with water, soap (or a neutral detergent) and some form of mechanical action (brushing or scrubbing) removes and reduces dirt, debris and other organic matter such as blood, secretions and excretions, but does not kill microorganisms.

In addition to the methodology used, the disinfectant concentration and contact time are also critical for effective surface disinfection.

Disinfectant solutions must be prepared and used according to the manufacturer's recommendations for volume and contact time.

Enough disinfectant solution should be applied to allow surfaces to remain wet and untouched long enough for the disinfectant to inactivate pathogens, as recommended by the manufacturer.

Training in health-care settings

Training the staff is the major challenge we come across in the health care setting , induction training , pre and post training examination, posters, mock drills and reminders are the best way of

implementation.

Environmental cleaning is a complex infection prevention and control intervention that requires a multipronged approach, which may include training, monitoring, auditing and feedback, reminders and displaying SOPs in key areas.

In health-care facilities and public buildings, posters or other guidance should be visible to cleaning workers and others to guide and remind them about the proper procedures on disinfectant preparation and use

Cleaning and disinfection techniques and supplies

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 in a systematic manner to avoid missing any areas.

Cleaning equipment (e.g. buckets) should be well maintained. Equipment used for isolation areas for patients with COVID19 should be colour-coded and separated from other equipment

Follow the manufacturer's instructions to ensure that disinfectants are prepared and handled safely, wearing the appropriate personal protective equipment (PPE) to avoid chemical exposure.

The selection of disinfectants should meet local authorities' requirements for market approval, and needs Infection control committee approval.

The use of chlorine-based products

Hypochlorite-based products include liquid (sodium hypochlorite), solid or powdered (calcium hypochlorite) formulations. Hypochlorite displays a broad spectrum of antimicrobial activity and is effective against several common pathogens at various concentrations. For example, hypochlorite is effective against rotavirus at a concentration of 0.05% (500 ppm), however, higher concentrations of 0.5% (5000 ppm) are required for some highly resistant pathogens in the health-care setting such as C. auris and C. difficile

The recommendation of 0.1% (1000 ppm) in the context of COVID-19 is a conservative concentration

that will inactivate the vast majority of other pathogens that may be present in the health-care setting. However, for blood and body fluids large spills (i.e. more than about 10mL) a concentration of 0.5% (5000 ppm) is recommended.

Hypochlorite is rapidly inactivated in the presence of organic material; therefore, regardless of the concentration used, it is important to first clean surfaces thoroughly with soap and water or detergent using mechanical action such as scrubbing or friction

Calculation of sodium hypochlorite concentrations

[% chlorine in liquid sodium hypochlorite " % chlorine desired] " 1 = Total parts of water for each part sodium hypochlorite.

Ex: [5% in liquid sodium hypochlorite/ 0.5% chlorine desired] -1 = 9 parts of water for each part sodium hypochlorite

Spraying disinfectants and other no-touch methods

In indoor spaces, routine application of disinfectants to environmental surfaces by spraying or fogging (also known as fumigation or misting) is not recommended for COVID19.

These technologies supplement but do not replace the need for manual cleaning procedures.

Spraying or fumigation of outdoor spaces, such as streets or marketplaces, is also not recommended to kill the COVID-19 virus or other pathogens because disinfectant is inactivated by dirt and debris and it is not feasible to manually clean and remove all organic matter from such spaces.

Spraying individuals with disinfectants (such as in a tunnel, cabinet, or chamber) is not recommended under any circumstances. This could be physically and psychologically harmful and would not reduce an infected person's ability to spread the virus through droplets or contact (Table 3)

Personal safety when preparing and using disinfectants

Cleaners should wear adequate personal protective

equipment (PPE) and be trained to use it safely.

Protect Yourself and Other Cleaning Staff

- Ensure cleaning staff are trained on proper use of cleaning (and disinfecting, if applicable) products.
- Read the instructions on the product label to determine what safety precautions are necessary while using the product. This could include PPE (such as gloves, glasses, or goggles), additional ventilation, or other precautions.
- Wash your hands with soap and water for 20 seconds after cleaning. Be sure to wash your hands immediately after removing gloves.
 - o If hands are visibly dirty, always wash hands with soap and water.
 - o If soap and water are not available and hands are not visibly dirty, use an alcohol-based hand sanitizer that contains at least 60% alcohol, and wash with soap and water as soon as you can.

Social Distancing Stops the Spread of Disease

Some viruses – like the virus that causes COVID-19 – spread easily, according to the CDC and many other . Social distancing puts space between individuals. If someone is sick and there are no people around, a virus cannot spread.

“Social distancing means we are doing our best to stay away from people so as to limit the spread of coronavirus,”

How to Practice Social Distancing

Tactics for social distancing include canceling large social gatherings, such as sports events and concerts, as well as closing schools, bars and restaurants, and having people work from home instead of an office. But it also means limiting any interaction with anyone beyond your immediate family, with whom you live.

What to Do If You Must Leave Home

While working from home is recommended, some people don't have that option. And you may have to run out to the grocery store or pharmacy. In these cases, practice vigilant Hand hygiene and stay at least 6 feet away from other people.

Table 3 : Health-care setting : Recommended frequency of cleaning of environmental surfaces, according to the patient areas with suspected or confirmed COVID-19 patients.

Patient area	Frequency ^a	Additional guidance
Screening/triage area	At least twice daily	<ul style="list-style-type: none"> • Focus on high-touch surfaces, then floors (last)
Inpatient rooms / cohort – occupied	At least twice daily, preferably three times daily, in particular for high-touch surfaces	<ul style="list-style-type: none"> • Focus on high-touch surfaces, starting with shared/common surfaces, then move to each patient bed; use new cloth for each bed if possible; then floors (last)
Inpatient rooms – unoccupied (terminal cleaning)	Upon discharge/transfer	<ul style="list-style-type: none"> • Low-touch surfaces, high-touch surfaces, floors (in that order); waste and linens removed, bed thoroughly cleaned and disinfected
Outpatient / ambulatory care rooms	After each patient visit (in particular for high-touch surfaces) and at least once daily terminal clean	<ul style="list-style-type: none"> • High-touch surfaces to be disinfected after each patient visit • Once daily low-touch surfaces, high-touch surfaces, floors (in that order); waste and linens removed, examination bed thoroughly cleaned and disinfected
Hallways / corridors	At least twice daily ^b	<ul style="list-style-type: none"> • High-touch surfaces including railings and equipment in hallways, then floors (last)
Patient bathrooms/ toilets	Private patient room toilet: at least twice daily Shared toilets: at least three times daily	<ul style="list-style-type: none"> • High-touch surfaces, including door handles, light switches, counters, faucets, then sink bowls, then toilets and finally floor (in that order) • Avoid sharing toilets between staff and patients

Environmental surfaces should also be cleaned and disinfected whenever visibly soiled or if contaminated by a body fluid (e.g., blood); ^b Frequency can be once a day if hallways are not frequently used.

What to do to keep yourself and others safe from COVID-19

- **Maintain at least a 1-metre distance between yourself and others** to reduce your risk of infection when they cough, sneeze or speak. Maintain an even greater distance between yourself and others when indoors. The further away, the better.
- **Make wearing a mask a normal part of being around other people. The appropriate use, storage and cleaning or disposal are essential to make masks as effective as possible.**

Disinfect Safely When Needed

If you determine that regular disinfection may be needed

- If your disinfectant product label does not specify that it can be used for both cleaning and disinfection, clean visibly dirty surfaces with soap or detergent before disinfection.
- **Always follow the directions on the label** to ensure safe and effective use of the product. The label will include safety information and application instructions. Keep disinfectants out of the reach of children. Many products recommend keeping the surface wet with a disinfectant for a certain period (see "contact time" on the product label).
- Check the product label to see what PPE (such as gloves, glasses, or goggles) is required based on potential hazards.
- Ensure adequate ventilation (for example, open windows).
- Use only the amount recommended on the label.
- If diluting with water is indicated for use, use

water at room temperature (unless stated otherwise on the label).

- Label diluted cleaning or disinfectant solutions.
- Store and use chemicals out of the reach of children and pets.
- Do not mix products or chemicals.
- Do not eat, drink, breathe, or inject cleaning and disinfection products into your body or apply directly to your skin. They can cause serious harm.
- Do not wipe or bathe people or pets with any surface cleaning and disinfection products.

5 Steps for Safe & Effective Disinfectant Use:

Step 1: Check that your product is approved

Find the registration number on the product.

Step 2: Read the directions Follow the product's directions. Check "use sites" and "surface types" to see where you can use the product. Read the "precautionary statements."

Step 3: Pre-clean the surface

Make sure to wash the surface with soap and water if the directions mention pre-cleaning or if the surface is visibly dirty.

Step 4: Follow the contact time

You can find the contact time in the directions. The surface should remain wet the whole time to ensure the product is effective.

Step 5: Wear gloves and wash your hands

For disposable gloves, discard them after each cleaning. For reusable gloves, dedicate a pair to disinfecting COVID-19. Wash your hands after removing the gloves.

The Story of the Mask and its Importance during the COVID-19 pandemic



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In the early 1900s, the word 'operation theatre' literally meant a theatre where medical students could go and watch a surgery being performed by the senior Surgeons. The Chief Surgeon would be assisted by Assistant Surgeons and nurses. Nobody wore gloves or a mask, as the importance of these were not known then (Figure 1). As the surgeon performed his surgery under the powerful overhead operating lights, he spoke loudly about what he was dissecting so that the students sitting in the amphitheatre understood what he was doing.

During one of those days in 1903 at one of the large teaching hospitals in Chicago, a group of medical students were sitting in the amphitheatre watching the surgery. One of the students while gazing through the powerful operating light that was focussed on the operation site observed something very unusual. While the surgeon spoke, in the backdrop of the powerful rays of light, he saw a spray of liquid coming out of the surgeon's mouth and falling slowly on the patient who was being operated. The louder he spoke, the more spray came out of his mouth. Being disturbed by what he saw, he talked about this to one of his teachers, Dr Alice Hamilton, one of the renowned physicians of that time, and asked her 'shouldn't surgeons cover their mouth when they performed surgeries to prevent the mouth spray from falling onto the surgical site?' Alice Hamilton (Figure 2) was visibly disturbed by this feedback from the student and decided to perform a study to investigate this.

Instead of the patient on the operating table, she kept petri dishes containing culture media in them and requested the surgeon to talk what he normally talked while performing surgery. At the end of the 'sham surgery' she collected the microbial plates and cultured them in the microbiology laboratory. To her surprise, she made some fascinating

observations: (1) An average of 75 bacterial colonies were identified in the culture plate which grew Streptococci, Diplococci, Staphylococci and Sarcine. Half of them were virulent when injected into guinea pigs, (2) Antiseptic mouth washes were of no use, (3) Talking released droplets that travelled up to 24 cms, while with coughing it was 36 cms. Whispering produced more droplets than talking.

She concluded that the mouth of the surgeon was a fruitful source of bacterial infection even after usual precautions of disinfection and recommended that surgeons and nurses should cover their mouths while performing surgery. She published this seminal work in the Journal of American Medical Association in 1903 (1), but sadly, this was not taken very seriously by the surgical community.

The great Manchurian Plague that started in the city of Manchurian in China in 1910 killed around 50,000 people due to Pneumonia. Wu Lien-teh, a Malaysian born physician who had studied in Cambridge was deputed to help control the plague in Manchurian. He knew that the plague was transmitted by airborne droplets and in order to protect himself, he wore a 2 layered surgical gauze, which he called as the 'Plague Mask' (Figure 3). He was convinced that the gauze mask was protecting him from catching the infection and recommended that all physicians, nurses, and health care providers who were taking care of plague patients wore this mask. He also recommended all patients and lay people in the community also wear this mask (2). However, many people made fun of him saying that he looked like a bandit hiding his identity.

In 1918, Doust and Lyon from New York University performed a very interesting experiment to study the efficacy of different types of gauze (coarse, medium and fine or butter gauze) made up of 2 to

10 layers in filtering bacteria (3). They placed these gauzes over petri dishes that contained bacterial culture media. Petri dishes were kept at distances of 1, 2, 3, 4, 5, and 6 feet away from a healthy person who was asked to cough for 5 mins. They wanted to examine whether bacterial filtration efficacy improves with the type of gauze, number of layers of gauze and whether the distance from the source of cough had any impact on the number of bacterial colonies grown in the culture media. This brilliant experiment gave rise to novel observations (Figure 4): (1) The more the thread count (finer the gauze), the better was the bacterial filtration efficacy. The butter cloth was the most efficient in filtering the bacteria. (2) Filtration efficacy improved with increased numbers of layers of gauze, (3) The number of bacteria in the droplets reduced with increasing distance. This was perhaps one of the first studies that objectively reported the efficacy of gauze masks in filtering off bacteria.

In 1927, an important event occurred at the Presbyterian Hospital in New York. A series of severe hemolytic streptococcal post-operative wound infections were observed among operated patients, the source of which was not known. Based on the findings of Alice Hamilton 24 years earlier, a bacterial swab of the throat and nose was taken from all surgeons from the hospital who operated upon these patients. Surprisingly, or rather unsurprisingly, 33% harbored hemolytic streptococci in their throats, and many of them carried them in the nose as well, proof that the source of the post-operative wound infections originated from the surgeon's mouth. None of the surgeons had shown any signs of upper respiratory tract infection. The results were reported in the Journal of American Medical Association (4) and based on this experience, a strict advisory was given to all surgeons, nurses and other operating staff members to wear a mask during surgery. That is why surgeons wear a mask – primarily to protect the patient on whom they are operating from being infected by bacteria from the surgeon's mouth and nose.

The surgical mask is made up of 3 different layers. The outer layer is made up of a hydrophobic layer of non-woven material. It prevents, blood, water or other body fluids from passing into the surgeon's

mouth and nose while he is operating. The middle layer is made up of melt-blown filter, which filters dust particles, bacteria and viruses efficiently. The inner layer is made up of a soft absorbent non-woven material that helps in absorbing sweat. Non-woven material is generally better than woven material for filtration. A good quality surgical mask fits well, does not allow blood, other body fluids and microbes (bacteria, fungi and viruses) to pass through, does not make breathing difficult, is non-inflammable and more importantly, does not allow droplets generated from the mouth and nose (during talking, shouting, singing, coughing, sneezing) to go outside. A surgical mask can be worn only once for a duration of 4 to 6 hours, after which it needs to be discarded carefully. Sadly, a lot of people wear the same mask for several days.

It is important to appreciate that a mask is worn primarily to prevent others from catching your infection. Of lesser importance, is to protect you from catching others infection. During the COVID-19 pandemic, masks have to be worn exactly for this reason. If the infected person does not wear a mask, nor does the other person in close contact, the risk of catching the infection is around 90%. If the infected person does not wear a mask and the person in close contact does, the risk of catching the infection is reduced to 30%. On the other hand, if the infected person wears a mask, the risk of the other person catching the infection even when that person does not wear a mask is only 5%. Finally, if both wear a mask, the risk of transmitting the infection is <1.5% even when they are in close vicinity to one another (Figure 5). These risks are only estimates, but drive home an important point for why one should wear a mask during the COVID pandemic.

What is an N95 mask?

Most surgeons would have heard about the N95 mask, but very few actually know what it means. The National Institute for Occupational Safety and Health (NIOSH), which is a division of the Centers for Disease Control (CDC) was given the responsibility by the US Government to lay down standards for the quality and type of mask that need to be worn in dusty occupations. Oil-based particles, such as those coming from sealants,

lubricants and coolants are very difficult to filter. Those masks that do not allow any oil particles to pass through are called 'oil proof' or 'P' masks, those that allow some 'resistance' are called 'R' masks and those that allow oil particles to pass through are called 'not resistant to oil' or 'N'. That is where the word 'N' originates from. Each of the N, R and P masks are further divided into 95, 99 and 100, such that the N95 mask filters off at least 95% of particles that are more than 0.3 microns, N99 filters at least 99% of particles and N100 filters 100% particles. Obviously the N100 mask is the most efficient mask for filtering non-oily particles, but they are the most uncomfortable to wear in terms of breathability, N99 is slightly better to breathe, and the N95 mask is relatively the easiest to breathe. Filtration efficacy and breathability do not go hand in hand, you have to compromise somewhere, and that is where N95 becomes the mask that is easy to breathe, yet offer over 95% protection. The N95 mask needs to be worn tightly in order to have maximum filtration efficacy, but some people find even these masks difficult to breathe through after a while, especially those with underlying asthma or heart disease. These masks were primarily meant for dusty occupations where people spent several hours. Some masks were built with a valve to make breathing out easier, as the valve allowed only exhaled air to pass outside easily which did not need filtration.

The N95 mask filters particles more than 300 nanometers (0.3 microns) efficiently. However, viruses are in the size range of 90-120 nanometers, but surprisingly are very easily filtered by the N95 mask, because particles less than 300 nanometers, deposit by Brownian motion. The N95 mask, in fact, filters particles less than 0.3 microns more efficiently than those that are more than 0.3 microns. This was the scientific basis for its use during the earlier SARS epidemic, but became more popular during the current COVID-19 pandemic.

N95 masks are useful masks to both prevent and protect from COVID infection, but it is important to ensure that the valved mask if not used. If used by an infected individual who may be symptomatic, the valved mask allows exhaled air to pass out without filtration and therefore allows the spread

of the SARS-CoV-2 virus to spread in the air. Sadly, a lot of people not only in India, but across the world wore and still continue to wear the valved N95 mask. Infected people wearing an N95 mask will spread the infection around. An advisory against the use of the valved N95 mask was given finally by the Ministry of Health and Family Welfare, Government of India on the 20th July 2020. Only ICU personnel who wear the full PPE and N95 mask for several hours everyday may be allowed to use the valved N95 mask, only to improve their breathability, with the hope they are not asymptomatic carriers and therefore not transmitting infections in the ICU setting. The N95 mask should be used only once and discarded safely the same day.

Cloth Masks:

When the COVID-19 pandemic started, there was a severe shortage of masks. Even the medical community could not get access to proper masks while they were taking care of the COVID-19 patients. During the early part, the WHO made a recommendation that only healthcare providers should wear a mask, a wrong advisory, which was soon corrected. On 30th March, 2020, the Principal Scientific Advisor to the Prime Minister of India released a manual on home-made masks and recommended that everybody should wear a home-made cloth mask. Although it suggested the use of multiple layers, there was no good scientific evidence to support this. It was not until a few weeks later that Konda and colleagues from the School of Molecular Engineering, University of Chicago, reported their results of the filtration efficacy of different types of cloth masks. They compared cotton, silk, chiffon, flannel and a combination of these materials in filtering off particles that were less than 300 nm and more than 300 nm (6).

They reported 2 important observations: (1) If a mask is not worn properly, its filtration efficacy reduces dramatically, (2) some cloth masks offer similar filtration efficacy as the surgical mask and the N95 mask. Masks made up of cotton quilt, cotton and silk, cotton and chiffon and cotton and flannel were as good, if not better than the surgical/ N95 mask in filtering particles less than 0.3 microns. This study offers scientific evidence to support the

use of cloth masks for COVID-19. Two cotton layers (thread per inch of at least 400) with either a silk or chiffon layer in the middle appears to be an appropriate cloth mask, at least as of now. They are not only easy to make and cheap, but are also reusable after daily washing and are comfortable to wear.

Mathematical models have suggested that if all people wear a mask during the COVID pandemic, the transmission and spread of the disease can be significantly halted. It is important to wear the right mask and wear it properly. We all now need to start getting used to wearing masks and make it a part of our culture if we want to get rid of this COVID-19 pandemic.

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Figure 1: Surgery amphitheatre during 1903. Notice surgeons not wearing gloves and masks.



Figure 2: Dr Alice Hamilton (1903) who performed one of the first experiments to show that during surgery, surgeons spray droplets infected with bacteria onto the patients' operation site.



Figure 3: The Plague Mask that became popular during the Manchurian plague of 1910

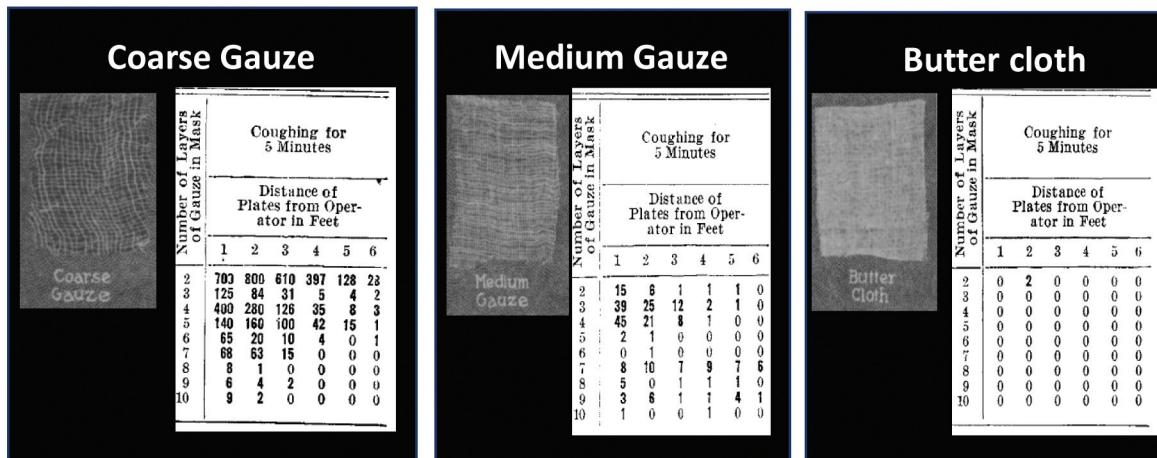


Figure 4: Efficacy of different types of gauze on bacterial filtration



Figure 5: Risk of transmission of COVID-19 depending on who wears a mask. The subject on the left is COVID-19 infected and the one on the right is un-infected.

	<300nm	>300nm
N95 Worn properly	85 ± 15%	99.9%
N95 Not worn properly	34 ± 15%	12%
Surgical Mask (No gap)	76 ± 22%	99.6%
Surgical Mask (gap)	50 ± 70%	44%
	<300nm	
Cotton Quilt	96 ± 2%	
Cotton 80TPI 1 layer	9 ± 13%	
Cotton 80TPI 2 layers	38 ± 11%	
Cotton 600TPI 1 layer	79 ± 23%	
Cotton 600TPI 2 layers	82 ± 19%	
Flannel	57 ± 8%	
Chiffon 1 layer	67 ± 16%	
Chiffon 2 layers	83 ± 9%	
Natural silk 1 layer	54 ± 8%	
Natural silk 2 layers	65 ± 10%	
Cotton + Chiffon	97 ± 2%	
Cotton + Flannel	95 ± 2%	
Cotton + Silk No gap	94 ± 2%	
Cotton + Silk Gap	37 ± 7%	

Figure 6: Comparison of N95 and Surgical masks versus cloth masks (Konda et al, ACS Nano, 2020, ahead of print)

Dilemmas and Challenges in Managing COVID 19



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The SARS-CoV2 pandemic which broke out nearly two years ago has challenged the medical, administrative, political, social and educational infrastructures across the world, while challenging financial strengths of all the sectors. Despite this, even today, no definitive therapy can be offered to patients infected with the virus. Several drugs have been used "off label" and others have been "repurposed" in the hope of finding the magic bullet which has remained elusive. The development of vaccines for SARS CoV2 and their release have been unprecedentedly quick, offering a ray of hope. Clinicians dealing with patients infected with the virus are always faced with dilemmas regarding the treatment making the management of this perplexing disease even more challenging.

The various dilemmas facing the clinicians begin from the time of presentation with initial symptoms. The diagnostic tests to be used, the markers of severity, the role of CT scan, therapeutic options available, the mode of oxygen delivery to be used and the role of the newly available "covid cocktail" are all among the list of dilemmas faced. In addition, with the increasing number of vaccine types available, the choice of vaccine to be advised is also a point to consider. This review seeks to weigh the current evidence available to overcome some of these dilemmas.

CLINICAL PRESENTATION:

The clinical presentation of COVID 19 is well known now. Although no specific clinical features are specific for COVID 19, a combination of fever, myalgia, sore throat and loss of sense of taste and smell seemed to be consistent features when the pandemic started. In a tropical country like ours, fever and myalgia are witnessed in most fevers. Loss of taste and smell appeared to be consistently

associated with SARS CoV2 infection during the first wave. However, during the second wave, the clinical presentation seemed to have changed with the arrival of the Delta strain. Persistent dry cough was now the most consistent feature. In addition, gastrointestinal manifestations like diarrhoea and abdominal discomfort were seen more often. The headache which accompanies most tropical infections had to be viewed with greater suspicion during COVID 19 with the increasing recognition of severe infection with Mucor ("Black Fungus"). In addition, younger patients who were more affected during the second wave, presented with thrombotic events related to coronary and cerebrovascular territories on a background of SARS CoV 2 infection. The myriad of new manifestations, especially during the second wave made the diagnosis of the infection a challenge. Moreover, the incidence of segmental and sub-segmental pulmonary thrombo-emboli also was higher during the second wave, adding to the diagnostic and therapeutic dilemma.

CYCLE THRESHOLD VALUE:

The "Gold Standard" for the definitive diagnosis of COVID 19 is the RT-PCR test. Different viral target genes have been used. These include the Spike(S), Nucleocapsid(N), Envelope(E), RNA dependent RNA polymerase (RdRp) and the open reading frame 1 (O) genes. The amplification needed for the target gene to cross the threshold is inversely related to the viral load¹. On a PCR test this threshold is represented by the Cycle Threshold value (Ct). It is believed that low Ct values imply higher viral load and therefore greater infectivity. Quantification of the viral load is therefore, expected to identify patients who are more infective and need longer period of isolation during treatment. This has been used as a guide in various guidelines to release patients from isolation. Whether this viral load

translates into higher severity of infection is not clear and remains a dilemma. In a prospective analysis in our centre², we observed a higher severity of disease and higher mortality among patients who had lower Ct values (higher viral loads) during the first wave. During the second wave, severe disease was seen even among those who had higher Ct values. However, in the interim period the cut off for a positive test was revised to 35 cycles from the previous threshold of 30 cycles. Some of these patients were vaccinated as well. The dilemma of the Ct value representing high viral loads therefore was confounded and continues to do so. It is probably more appropriate to accept that the severity of COVID 19 is only partially contributed to by the viral load.

ANTIBODY TESTING:

Testing for SARS CoV2 antibodies started within a few months of the beginning of the pandemic³. Initially, the recommendation was not to use the presence of antibodies as diagnostic of active disease. This recommendation seemed scientifically appropriate at that time. Soon after the first wave in late 2020, there seemed to be an increase in the number of patients who presented with arterial insufficiency (stroke, CAD, Peripheral Vascular disease) and testing positive for SARS CoV 2 antibodies, without antecedent history of COVID 19. This resulted in the dilemma of whether these patients were a separate cohort or was representative of the general incidence of asymptomatic infection in the community. This trend was noticed right through the first few months of 2021, when the vaccination drive began in the country. The number of patients who presented with various clinical syndromes, with variable levels of antibodies post vaccination has given rise to another set of dilemmas. First, are those with low antibody titres susceptible to infection with newer variants? The answer seems to be in the affirmative, since moderate disease was seen in the second wave, even among those who were fully vaccinated. Second, does the currently available antibody testing technology quantify the efficacy of the vaccines? The answer to this seems to be negative. Third, do these patients with low antibody titres qualify for a

booster dose of the vaccine? Opinion regarding this is divided in the scientific community and the dilemma persists. Lastly, do the patients with low titres benefit from the "cocktail"? Again, the answer is not definitive, but current recommendations seem to advise for the use of the cocktail.

COMPUTED TOMOGRAPHY SCAN:

The use of CT scan has risen in tandem with the spread of the pandemic. The knowledge about ground glass opacities has increased amongst all medical professionals apart from radiologists. Along with increased use of CT, several scoring systems began to be used. The first one that was widely accepted was developed by the Dutch Radiological Society – the COVID 19 Reporting and Data System (CORADS)⁴. While the first five categories correlated with the degree of suspicion, category 6 was solely based on a positive PCR test. As a result, it began to be interpreted in numerical sequence with patients correlating CORADS 6 as worse than CORADS 4/5, the CT images notwithstanding. This dilemma persisted till more pragmatic scoring systems evolved (Yang and Fleischner) which provided quantitative scores out of 40 and 25 respectively. Subsequently, significant data has accumulated correlating higher CT scores with higher levels of biomarkers and with more severe disease. However, judging the severity of the disease solely on the basis of a high CT score remains a dilemma. The timing of the scan and the relevance of aggressive therapy for a persistently severe CT appearance remains a clinical dilemma. While it is accepted that a CT (with contrast) may be repeated to diagnose pulmonary thromboembolism, routine repetition of scans when there is no clinical improvement remains a point of confusion. Given the paucity of therapeutic options available beyond the first week of illness, the relevance of a repeat CT scan seems to be limited to prognostication rather than for therapeutic guidance. The other dilemma arises when the repeat CT is indeed done suspecting an embolism. Pneumothoraces and pneumomediastinum have been reported in the second week of illness. While pneumothoraces can be drained, the therapeutic strategy for pneumo-mediastinum remains a dilemma especially among patients who are on non-

invasive ventilation. What happens to the pneumomediastinum once the patient is intubated remains a dilemma

BIOCHEMICAL TESTS:

Several biochemical tests have come into prominence during the two waves of COVID 19. Prime amongst them are the Neutrophil Lymphocyte Ratio (NLR), the D-Dimer, CRP and IL-6. The NLR was first reported to be a marker of severity amongst the earliest Chinese cohorts. The relative decrease in Neutrophil count normally seen in viral syndromes was reversed with SARS CoV2, and was considered as a diagnostic as well as a prognostic marker. Data that was published subsequently listed D-Dimer and CRP as significantly elevated in severe COVID 19. While CRP was an expected acute phase reaction, the role of D-Dimer and its elevation raised a lot of queries⁵. The first query seemed to be if D-Dimer was a marker of severe systemic inflammation or a marker of extensive vascular thrombi formation. This dilemma was further confounded by the recognition of significant incidence of PTE among critically ill COVID 19 patients. This was considered as an explanation for the so-called happy hypoxia among these patients. The second dilemma that arose was about the dose of anticoagulation required. Prophylactic doses were initiated in nearly all hospitalized patients, but escalation for those with rising values of D-Dimer remained and still is a grey zone in the management of COVID 19. The third query that arose with the recognition of D-Dimer as a marker of severe disease was the duration of anti-coagulation for those who had very high values with and without major vascular thrombosis. Most guidelines do mention weight based prophylactic doses for patients with elevated D-Dimer values. The guidelines however, do not favor increasing the dose of antithrombotic agents as a reaction to increasing D-Dimer values. Guidelines also do not recommend continuing the anticoagulation after discharge for those patients who did not have vascular thrombosis. The dilemma about the choice and duration of anticoagulation for who did have significant vascular thrombosis is yet to be resolved. The role of the IL-6 was even more of a dilemma⁶. During the first wave, lot of attention was focused on "Cytokine Storm" and IL-

6 was considered to be a major indicator of this phenomenon. Therapy targeted at IL-6 reduction including extra corporeal removal was attempted with no great success. Traditionally, inflammatory markers like IL-6 and CRP are known to be elevated in the alveolar fluid among patients invasively ventilated for ARDS. However, during the pandemic, very high levels of IL-6 were noted in the serum even among those who were not invasively ventilated. Finally, it does seem that elevated D-Dimer and IL-6 are phenomena associated with severe COVID 19 and keep pace with the disease progression or regression. Specific therapies targeted at lowering these two markers or as a reaction to their elevation, seems less likely to succeed.

DRUG THERAPY:

Three drugs got a lot of attention over the past two years as part of the treatment of COVID 19 - the repurposed drug Remdesivir, the immune modulator Tocilizumab and the corticosteroids Dexamethasone and Methylprednisolone.

Remdesivir appeared as the brightest hope during the first wave and initial results appeared to justify this hope. In a multinational randomized control trial (RCT) of Remdesivir vs Placebo for severe COVID 19, the authors demonstrated a significant reduction in the time to recovery. The benefit was clearest in the group requiring oxygen. However, the benefit was not obvious in those requiring HFNC/ NIV. Recovery was also not better amongst those who were on invasive ventilation or ECMO. In a study which excluded patients needing invasive ventilation or ECMO, or having MOF, clinical improvement was no different among those who received Remdesivir. A ten day course of Remdesivir was not found to be superior to a 5 day course in an RCT⁷. The recent RCT in the journal The Lancet also waters down the optimism with which Remdesivir is being prescribed. This gives rise to two therapeutic dilemmas. One, should Remdesivir still be prescribed for hospitalized patients and two, does a longer course confer any benefit? The answer to the second question is a definite no, while the first remains more of an ethical dilemma. This dilemma has been further confounded by the entry of Baricitinib – a selective

inhibitor of Janus kinase (JAK) 1 and 2 into the playing field. This drug is expected to modify the immune mediated damage caused by SARS-CoV2 infection by inhibiting the intracellular signaling pathway of cytokines known to be elevated in severe Covid-19, including interleukin-2, interleukin-6, interleukin-10, interferon- α , and granulocyte-macrophage colony stimulating factor. This drug generated much hope and was the subject of a recently published RCT¹³. This RCT compared the combination of Baricitinib and Remdesivir with Remdesivir alone for hospitalized patients requiring oxygen. This study demonstrated a benefit with use of the combination. However, since benefit with Remdesivir per se has been questioned, the dilemma of the drug being combined with another, providing better results confounds the issue.

Tocilizumab also enjoyed its place in the limelight especially during the first wave. The industry sponsored COVACTA phase 3 trial⁹ evaluating the effect of Tocilizumab on clinical improvement did not show a significant benefit in terms of need for invasive ventilation and intensive care. Observational and retrospective studies did show a benefit. But, the dilemma still remains regarding the strategy to be followed for an individual patient who is progressively hypoxic with worsening CT and rising biomarkers. The answer does not seem to be Tocilizumab, but what exactly helps is the dilemma.

Corticosteroids have also been a source of some dilemma in the treatment of COVID 19. Their potent anti-inflammatory properties make them an attractive option. The RECOVERY trial demonstrated a survival benefit amongst hypoxic patients treated with dexamethasone (6 mg per day for 10 days or till hospital discharge). The CODEX RCT was a multi-center open label RCT, evaluating the benefit of using dexamethasone in moderate to severe COVID 19 related ARDS. The primary endpoint was ventilator free days at 28 days, which was found to be significantly better in the dexamethasone group. The REMAP-CAP COVID 19 study¹⁰ and the CAPE-COVID trial evaluated the effect of Hydrocortisone among patients requiring cardiovascular and respiratory organ support. Both the studies failed to show any superiority for Hydrocortisone over standard therapy. The MET COVID trial evaluated

the effect of Methyl Prednisolone among patients hospitalized for COVID 19. The intervention was used for patients requiring oxygen supplementation. The primary outcome was 28 day mortality which was not influenced by the intervention. However, quite a few patients were prescribed Methyl Prednisolone especially those with severe and critical COVID 19. Needless to say this drug was one of the putative causative factors in the increased incidence of Mucor among COVID 19 patients. The dilemma regarding the use of steroids is with respect to the dose and duration. While standard guidelines have described the dose and duration of dexamethasone therapy, clinical dilemma remains about continuing the therapy longer and especially for those who have shown a clinical improvement. The issue of continuing steroids among those patients who remain febrile beyond the first week of infection has also been a source of dilemma. Case reports and series have documented some benefit with a longer course of steroids in this cohort, but this strategy is yet to figure in any major guideline.

HYPOXEMIA MANAGEMENT:

The predominant clinical challenge while treating COVID 19 patients is in managing the hypoxemia. The decision regarding the choice of oxygen delivery system to be used has to be balanced against the risk of aerosol exposure to the health care workers. The first wave witnessed lot of concern regarding the use of non-invasive ventilation (NIV) and high flow nasal oxygen (HFNO) – two devices which work very well in hypoxic respiratory failure. The concern was predominantly about aerosolization during the first wave. However, with experience of usage, this concern took a back seat. Two new dilemmas emerged instead. One was about high oxygen consumption with HFNO and the other was the phenomenon of Patient Self Induced Lung Injury (P-SILI) with NIV¹¹. The marked disparity in oxygen demand and supply across the world was more prominent during the second wave. The high flow rates of HFNO mandate a higher consumption, making the use of this physiologically good device inefficient. The decision to use the device is still a dilemma especially if invasive ventilation is not an option. The increased ventilatory drive triggered by hypoxia is usually associated with high inspiratory

tidal volumes. This is witnessed even when the patient is initiated on positive pressure ventilation. The high respiratory rates and tidal volumes are postulated to trigger a cascade of inflammation, perpetuating the spread of alveolar damage. This has been designated P-SILI. Spontaneous modes like NIV may hypothetically be associated with a higher incidence of P-SILI. Therefore, denial of an accepted form of therapy for hypoxemia on this assumption remains a decision-making dilemma.

VACCINES:

Lastly, the dilemma regarding which vaccine to advise needs to be mentioned¹². At a time when the choice was limited to two types, availability was the only factor. However, as more options emerged and production ramped up, the dilemmas which seem to arise are

- i) Which vaccine protects against the Delta variant?
- ii) Is a booster dose needed?
- iii) Are the vaccines safe in pregnancy?
- iv) Can two different vaccines be combined?

Data available so far does not seem to indicate that one vaccine is superior to the other in protecting against the Delta variant, provided the 2 dose schedule has been completed. The point to be remembered however is that the currently available vaccines do not prevent infection but rather decrease the severity of manifestations. Data is not very robust to suggest that all vaccines need a booster. The dilemma is whether the currently available antibody tests reliably identify those who do not need a booster. Safety in pregnancy does not seem to be an issue and vaccination is recommended. Scientific rationale and opinion is divided over the combining of vaccines for better immune response.

In conclusion, treatment of COVID 19 has presented several challenges and thrown up quite a few dilemmas. Knowledge regarding this disease is still evolving and a definitive therapy is yet to emerge. Till then vaccination and safety precautions are the only hope.

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SARS-CoV-2 Variants



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All viruses, including SARS-CoV-2, the virus that causes COVID-19, change over time. Most changes have little to no impact on the virus' properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

WHO, in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. During late 2020, the emergence of variants that posed an increased risk to global public health prompted the characterisation of specific Variants of Interest (VOIs) and Variants of Concern (VOCs), in order to prioritise global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic.

WHO and its international networks of experts are monitoring changes to the virus so that if significant amino acid substitutions are identified, we can inform countries and the public about any changes that may be needed to respond to the variant, and prevent its spread. Globally, systems have been established and are being strengthened to detect "signals" of potential VOIs or VOCs and assess these based on the risk posed to global public health. National authorities may choose to designate other variants of local interest concern.

Reducing transmission through established and proven disease control methods measures, as well as avoiding introductions into animal populations, are crucial aspects of the global strategy to reduce the occurrence of mutations that have negative public health implications.

Current strategies and measures recommended by WHO continue to work against virus variants identified since the start of the pandemic.

Naming SARS-CoV-2 variants

The established nomenclature systems for naming and tracking SARS-CoV-2 genetic lineages by GISAID, Nextstrain and Pango are currently and will remain in use by scientists and in scientific research. To assist with public discussions of variants, WHO convened a group of scientists from the WHO Virus Evolution Working Group (now called the Technical Advisory Group on Virus Evolution), the WHO COVID-19 reference laboratory network, representatives from GISAID, Nextstrain, Pango and additional experts in virological, microbial nomenclature and communication from several countries and agencies to consider easy-to-pronounce and non-stigmatising labels for VOI and VOC. At the present time, this expert group convened by WHO has recommended using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma, Delta which will be easier and more practical to be discussed by non-scientific audiences.

Variants of Concern (VOC)

Working definition:

A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
- Increase in virulence or change in clinical disease presentation; OR
- Decrease in effectiveness of public health and

social measures or available diagnostics, vaccines, therapeutics.

Currently designated Variants of Concern (VOCs)⁺:

WHO LABEL	PANGO LINEAGE *	GISAID CLADE	NEXTSTRA IN CLADE	ADDITIONAL AMINO ACID CHANGES MONITORED°	EARLIEST DOCUMENTED SAMPLES	DATE OF DESIGNATION
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y. V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y. V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617 .2	G/478K.V 1	21A, 21I, 21J	+S:417N +S:484K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021
Omicron*	B.1.1.52 9	GR/484A	21K	-	Multiple countries, Nov-2021	VUM: 24-Nov-2021 VOC: 26-Nov-2021

*see TAG-VE statement issued on 26 November 2021 ° only found in a subset of sequences

Variants of Interest (VOI)

Working definition

A SARS-CoV-2 variant:

- with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND
- Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

WHO LABEL	PANGO LINEAGE*	GISAID CLADE	NEXTSTRAIN CLADE	EARLIEST DOCUMENTED SAMPLES	DATE OF DESIGNATION
Lambda	C.37	GR/452Q.V1	21G	Peru, Dec-2020	14-Jun-2021
Mu	B.1.621	GH	21H	Colombia, Jan-2021	30-Aug-2021

*Includes all descendent lineages. See the cov-lineages.org and the Pango network websites for further details.

Currently designated Variants of Interest (VOIs):

Reclassifying VOIs/ VOCs

A previously designated Variant of Interest (VOI) or Variant of Concern (VOC) which has conclusively demonstrated to no longer pose a major added risk to global public health compared to other circulating SARS-CoV-2 variants, can be reclassified.

This is undertaken through a critical expert assessment, in collaboration with the Technical Advisory Group on Virus Evolution of several criteria, such as the observed incidence/relative prevalence of variant detections among sequenced samples over time and between geographical locations, the presence/absence of other risk factors, and any ongoing impact on control measures.

Mutation Profiles of VOC/VOIs

As part of WHO's assessment of circulating variants, a clear understanding of the amino acid substitutions that are characteristic of each variant is needed. In collaboration with Erasmus Medical Centre the below table was assembled to summarize the spike protein amino acid changes for the current VOCs and VOIs. For each variant, the profile of amino acid changes in the Spike protein was created

based on the first 1,000 genomes available in GISAID (genomes with less than 29,000 nucleotides and >5% Ns were excluded). Amino acid changes that are present in e" 85% of the sequences are shown. Of note, relevant amino acid changes may be present in other regions of the SARS-CoV-2 genome, and not all amino acid changes in the spike protein are associated to potential changes in the characteristics of the virus variant. (Figure 1)

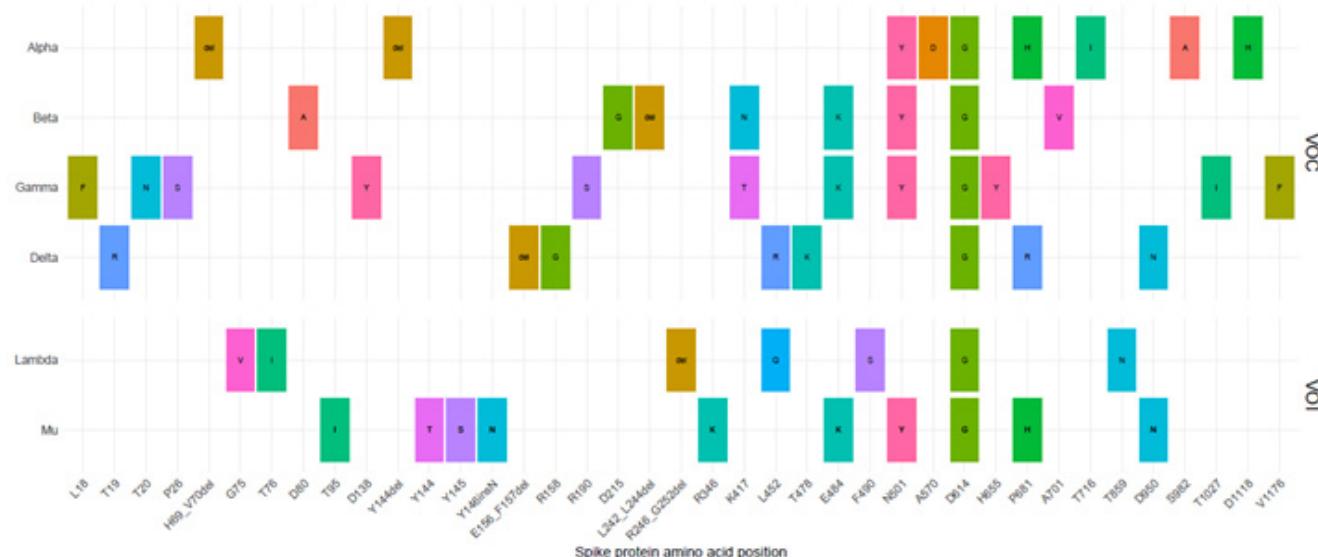
Variants Under Monitoring (VUM)

Working definition

A SARS-CoV-2 variant with genetic changes that are suspected to affect virus characteristics with some indication that it may pose a future risk, but evidence of phenotypic or epidemiological impact is currently unclear, requiring enhanced monitoring and repeat assessment pending new evidence.

Note: It is expected that our understanding of the impacts of these variants may fast evolve, and designated Variants under Monitoring may be readily added/removed; therefore, WHO labels will not be assigned at this time. Former VOIs/ VOCs may, however, be monitored for an extended period under this category, and will maintain their assigned WHO label until further notice.

Figure 1



Currently designated Variants Under Monitoring

PANGO LINEAGE*	GISAID CLADE	NEXTSTRAIN CLADE	EARLIEST DOCUMENTED SAMPLES	DATE OF DESIGNATION
AZ.5 [#]	GR	-	Multiple countries, Jan-2021	VUM: 02-Jun-2021
C.1.2	GR	-	South Africa, May 2021	01-Sep-2021
B.1.617.1 ^{\$}	G/452R.V3	21B	India, Oct-2020	VOI: 4-Apr-2021 VUM: 20-Sep-2021
B.1.526 ^{\$}	GH/253G.V1	21F	United States of America, Nov-2020	VOI: 24-Mar-2021 VUM: 20-Sep-2021
B.1.525 ^{\$}	G/484K.V3	21D	Multiple countries, Dec-2020	VOI: 17-Mar-2021 VUM: 20-Sep-2021
B.1.630	GH	-	Dominican Republic, Mar-2021	12-Oct-2021
B.1.640	GH/490R	-	Republic of Congo, Sep-2021	22-Nov-2021

*Includes all descendent lineages. See the cov-lineages.org and the Pango network websites for further details.

[#]formerly tracked under parent lineage B.1.1.318 ^{\$}Former VOIs: Kappa: B.1.617.1; Iota: B.1.526; Eta: B.1.525

Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern

The Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) is an independent group of experts that periodically monitors and evaluates the evolution of SARS-CoV-2 and assesses if specific mutations and combinations of mutations alter the behaviour of the virus. The TAG-VE was convened on 26 November 2021 to assess the SARS-CoV-2 variant: B.1.1.529.

The B.1.1.529 variant was first reported to WHO from South Africa on 24 November 2021. The epidemiological situation in South Africa has been characterized by three distinct peaks in reported cases, the latest of which was predominantly the Delta variant. In recent weeks, infections have increased steeply, coinciding with the detection of B.1.1.529 variant. The first known confirmed B.1.1.529 infection was from a specimen collected on 9 November 2021.

This variant has a large number of mutations, some of which are concerning. Preliminary evidence suggests an increased risk of reinfection with this variant, as compared to other VOCs. The number of cases of this variant appears to be increasing in almost all provinces in South Africa. Current SARS-CoV-2 PCR diagnostics continue to detect this variant. Several labs have indicated that for one widely used PCR test, one of the three target genes is not detected (called S gene dropout or S gene target failure) and this test can therefore be used as marker for this variant, pending sequencing confirmation. Using this approach, this variant has been detected at faster rates than previous surges in infection, suggesting that this variant may have a growth advantage.

Based on the evidence presented indicative of a detrimental change in COVID-19 epidemiology, the TAG-VE has advised WHO that this variant should be designated as a VOC, and the WHO has designated B.1.1.529 as a VOC, named Omicron.

SARS-CoV-2 Variant-Omicron

What is Omicron and what makes it a variant of concern (VoC)?

It is a new variant of SARS-CoV-2 that has recently been reported from South Africa on 24th November 2021 called as B.1.1.529 or Omicron (based on Greek alphabets like alpha, beta, delta etc). This variant has shown a very large number of mutations, especially more than 30 on the viral spike protein, which is the key target of the immune response. Given the collection of mutations in Omicron, which earlier individually have been associated with increased infectivity and/or immune evasion, and the sudden rise in number of positive cases in South Africa, World Health Organization has declared Omicron as a Variant of Concern (VoC).

Can the currently used diagnostics methods, detect Omicron?

The most accepted and commonly used method of diagnostic for SARS-CoV2 Variant is RT-PCR method. This method detects specific genes in the virus, such as Spike (S), Enveloped (E) and Nucleocapsid (N) etc to confirm the presence of virus. However, in case of Omicron, as the S gene is heavily mutated, some of the primers may lead to results indicating absence of the S gene (called as S gene drop out). This particular S gene drop out along with the detection of other viral genes could be used a diagnostic feature of Omicron. However, for final confirmation of the omicron variant genomic sequencing is required.

How concerned should we be about the new VoC?

WHO declares a variant as a VoC after assessment when there is increase in transmissibility or detrimental change in COVID-19 epidemiology; OR increase in virulence or change in clinical disease presentation; OR decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. (Source: WHO) It is important to highlight that Omicron has been declared VoC based on the observed mutations, their predicted features of increased transmission and immune evasion, and preliminary evidence of detrimental change in COVID-19 epidemiology, such as increased reinfections. The definitive evidence for increased remission and immune evasion is awaited.

What precautions should we take?

The precautions and steps to be taken remain same as before. It is essential to mask yourself properly, take both doses of vaccines (if not yet vaccinated), maintain social distancing and maintain good ventilation to the maximum possible.

Will there be a third wave?

Omicron cases are increasingly being reported from countries outside of South Africa and given its characteristics, it is likely to spread to more countries including India. However, the scale and magnitude of rise in cases and most importantly the severity of disease that will be caused is still not clear. Further, given the fast pace of vaccination in India and high exposure to delta variant as evidenced by high seropositivity, the severity of the disease is anticipated to be low. However, scientific evidence is still evolving.

Will the existing vaccines work against Omicron?

While, there is no evidence to suggest that existing vaccines do not work on Omicron, some of the mutations reported on Spike gene may decrease the efficacy of existing vaccines. However, vaccine protection is also by antibodies as well as by cellular immunity, which is expected to be relatively better preserved. Hence vaccines are expected to still offer protection against severe disease and, vaccination with the available vaccines is crucial. If eligible, but not vaccinated, one should get vaccinated.

Why do variants occur?

Variants are normal part of evolution and as long as the virus is able to infect, replicate and transmit, they will continue to evolve. Further, not all variants are dangerous and most often than not, we don't notice them. Only when they are more infectious, or can reinfect people etc they gain prominence. The most important step to avoid generation of variants is to reduce the number of infections.

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Past National President IMA

INDIAN SCENARIO

After the second wave, the daily average of COVID-19 cases in India is spiraling down, even though there still are isolated outbreaks and a rising positivity rate recorded in some states. However, despite this, there's some positive silver lining, which is the growing pace of vaccination in the country. While we may not be able to bid goodbye to COVID-19 as yet, it might be the time the viral outbreak may have reached a state of 'endemicity' in the country, given the rather low levels of transmission right now and the already largely exposed population in the country. But, with the virus very much an active threat, and possibilities of a potentially threatening third wave looking like an imminent threat, what does endemicity mean, in terms of COVID-19 spread, and how concerned should we be?

Ever since mutant variants of the virus have wreaked havoc and lowered the efficacy of vaccines, experts have pinpointed that achieving herd immunity, or removing COVID-19 from the world, altogether may not be actually possible. While we do know that certain mandates, such as testing, mask hygiene, distancing would still need to be followed till we know there's a low-graded risk, living while knowing that there's a virus forever could be very well a reality to acclimatize ourselves too.

While learning to live with COVID-19 forever does mean that the virus may never ever go away, however, it does mean that the virus, over time, may become less threatening and as higher rates of immunization are achieved, the virus would have fewer chances of spreading or spell severe outcomes, as we are seeing today. Several experts have also stressed that instead of trying for a zero-COVID-policy, transitioning from a pandemic to an endemic is the best probable scenario we may have currently.

High immunization rates and vaccination speeds are needed to provide peak protection and limit COVID from spreading. As we move into the future course of months, where there's a possibility of seeing more mutations coming up, the current vaccines may be upgraded, or subjected to changes, which could help them offer more protection and efficiency than we currently have. There's also talk of booster shots right now, which may be suggested for those who are immuno-compromised.

In the future, COVID vaccination may also become an annual affair, much like flu vaccination and thus, with added immunity, it would our best shot of defense to mitigate the risks of COVID-19.

GLOBAL SCENARIO

The COVID-19 pandemic has been met by unequal responses in different countries and led to unequal impacts, with populations in Europe, the USA, and Latin America disproportionately impacted.

Science has uncovered much about SARS-CoV-2 and made extraordinary and unprecedented progress on the development of COVID-19 vaccines, but there is still great uncertainty as the pandemic continues to evolve. COVID-19 vaccines are being rolled out in many countries, but this does not mean the crisis is close to being resolved. We are simply moving to a new phase of the pandemic.

What emerges next will partly depend on the ongoing evolution of SARS-CoV-2, on the behaviour of citizens, on governments' decisions about how to respond to the pandemic, on progress in vaccine development and treatments and also in a broader range of disciplines in the sciences and humanities that focus both on bringing this pandemic to an end and learning how to reduce the impacts of future zoonoses, and on the extent to which the international community can stand together in its efforts to control COVID-19. Vaccines

alone, unless they achieve high population coverage, offer long-lasting protection, and are effective in preventing both SARS-CoV-2 transmission and COVID-19, will not end the pandemic or allow the world to return to "business as usual". Until high levels of global vaccine-mediated protection are achieved across the world, it could be catastrophic if measures such as mask wearing, physical distancing, and hand hygiene are relaxed prematurely.

Countries, communities, and individuals must be prepared to cope in the longer-term with both the demands and the consequences of living with such essential containment and prevention measures.

Many factors will determine the overall outcome of the pandemic. A nationalistic rather than global approach to vaccine delivery is not only morally wrong but will also delay any return to a level of "normality" (including relaxed border controls) because no country can be safe until all countries are safe. SARS-CoV-2 could continue to mutate in ways that both accelerate virus transmission and reduce vaccine effectiveness.

Vaccine hesitancy, misinformation, and disinformation could compromise the global COVID-19 response.

Naive assumptions about herd immunity, given the appearance of new and challenging SARS-CoV-2 variants, could seriously risk repeated outbreaks and recurrences. SARS-CoV-2 can probably never be globally eradicated, because of its presence in many animals (including cats and dogs) and because of incomplete vaccine coverage and variable degrees of immunological protection.

Hence, ongoing strategies to deal with the endemic presence of SARS-CoV-2 in populations over the long term will be needed. Furthermore, we do not yet know if, and when, revaccination with current or new COVID-19 vaccines will be required since the duration of immunological protection and the efficacy against emergent SARS-CoV-2 variants remain unknown. With such uncertainties, we should not assume that recent scientific progress on COVID-19 diagnostics, vaccines, and treatments will end the pandemic. The world is likely to have many more years of COVID-19 decision making ahead—there is no quick solution available at present.

The decisions of global agencies and governments, as well as the behaviors of citizens in every society, will greatly affect the journey ahead. There are many possible outcomes. At one extreme is the most optimistic scenario, in which new-generation COVID-19 vaccines are effective against all SARS-CoV-2 variants (including those that may yet emerge) and viral control is pursued effectively in every country in a coordinated effort to achieve global control. Even with international cooperation and adequate funding, this scenario would inevitably take a long time to achieve. The COVAX initiative is just an initial step towards addressing vaccine equity and global coordination for vaccine access, especially for lower income countries.

At the other extreme is a pessimistic scenario, in which SARS-CoV-2 variants emerge repeatedly with the ability to escape vaccine immunity, so that only high-income countries can respond by rapidly manufacturing adapted vaccines for multiple rounds of population re-immunization in pursuit of national control while the rest of the world struggles with repeated waves and vaccines that are not sufficiently effective against newly circulating viral variants. In such a scenario, even in high-income countries, there would probably be repeated outbreaks and the path to "normality" in society and business would be much longer. And there are many other intermediate or alternate scenarios.

Countries that have kept SARS-CoV-2 in check and countries where there are high levels of viral transmission will in time all probably reach a similar destination, even though their paths to arrive there will be quite different, because no countries can remain permanently isolated from the rest of the world. Unfortunately, countries working in isolation from each other and from global agencies will prolong the pandemic. A nationalistic rather than a global approach to COVID-19 vaccine availability, distribution, and delivery will make a pessimistic outcome much more likely. Additionally, unless countries work together to scale up prevention efforts, the risk of other pandemics, or other trans boundary disasters with similar consequences, including those fuelled by climate change, will remain a constant threat.

The International Science Council (ISC), as the independent, global voice for science in the broadest sense, believes it is crucial that the range

of COVID-19 scenarios over the mid-term and long-term is explored to assist our understanding of the options that will make better outcomes more likely. Decisions to be made in the coming months need to be informed not only by short-term priorities, but also by awareness of how those decisions are likely to affect the ultimate destination. Providing such analyses to policy makers and citizens should assist informed decision making.

In developing its COVID-19 Scenarios Project, the ISC has consulted with WHO and the UN Office for Disaster Risk Reduction. The ISC has established in February, 2021, a multidisciplinary Oversight Panel made up of globally representative world experts in relevant disciplines to work with a technical team to produce the scenario map. The Oversight Panel will report within 6–8 months to the global community on the possible COVID-19 scenarios that lie ahead over the next 3–5 years, and on the choices that could be made by governments, agencies, and citizens to provide a pathway to an optimistic outcome for the world.

There is a realistic expectation that the global effort in vaccination will bring the pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) under control. Nonetheless, uncertainties remain about the type of long-term association that the virus will establish with the human population and, in particular, whether corona virus disease 2019 (COVID-19) will become an endemic disease. Although the trajectory is difficult to predict, the conditions, concepts and variables that influence this transition can be anticipated. Persistence of SARS-CoV-2 as an endemic virus, perhaps with seasonal epidemic peaks, may be fuelled by pockets of susceptible individuals and waning immunity after infection or vaccination, changes in the virus through antigenic drift that diminish protection and re-entries from zoonotic reservoirs. Here we review relevant observations from previous epidemics and discuss the potential evolution of SARS-CoV-2 as it adapts during persistent transmission in the presence of a level of population immunity. Lack of effective surveillance or adequate response could enable the emergence of new epidemic or pandemic patterns from an endemic infection of SARS-CoV-2. There are key pieces of data that are urgently needed in order to

make good decisions; we outline these and propose a way forward.

Main Three possible scenarios of the future of COVID-19

The first—and most worrisome—scenario is that we will not gain rapid control of this pandemic and thus will face a future with ongoing manifestations of severe disease combined with high levels of infection that, in turn, could foster further evolution of the virus. Vaccinations and previous infection could achieve long-term herd immunity, but we will need a very broad application of vaccines worldwide combined with comprehensive disease surveillance by accurate and readily available diagnostic assays or devices.

A second and more likely scenario is the transition to an epidemic seasonal disease such as influenza. Effective therapies that prevent progression of COVID-19 disease (for example, monoclonal antibodies that reduce hospitalization and death by 70–85%) may bring the burden of SARS-CoV-2 infection to levels that are equivalent or even lower than influenza. However, we should remember that the annual mortality burden of influenza, in non-pandemic years, is estimated to be between 250,000 and 500,000 deaths, with up to 650,000 all-cause deaths globally, comprising around 2% of all annual respiratory deaths (two thirds among people who are 65 years and older). This is an extremely important health burden and equates to a relatively ‘optimistic’ view of the future of the COVID-19 pandemic.

A third scenario is the transition to an endemic disease similar to other human corona virus infections that have a much lower disease impact than influenza or SARS-CoV-2. There is, however, limited data on the global burden of disease by common human corona viruses and as noted in above, it is not possible to predict with confidence whether further adaptations of SARS-CoV-2 to humans will increase or decrease its intrinsic virulence.

To better predict which scenario is likely to emerge and to better equip the world with an appropriate response, we propose several key questions that need to be answered and critical tools that need to

be developed. These comprise gaps in our knowledge in terms of epidemiology, immunology and virology, and missing surveillance, prophylactic and therapeutic tools.

This pandemic has shown both the importance of initiatives in individual countries and the interdependence of the world, and the necessity of global cooperation for pandemic control. It is the investment by a limited number of countries that has led to the biomedical discoveries that have brought forward the tools to interrupt the spread of the pandemic. Yet, the lack of international structures for the implementation of these tools has brought into focus the disparities between advantaged and disadvantaged groups both within countries and between countries. This highlights the current inadequacies in healthcare delivery systems and access to new biomedical interventions. Global health leaders will need to be vigilant with respect to the trajectory of SARS-CoV-2 in the near future while assessing the strategies and approaches used in the pandemic to develop more effective structures and processes to ensure a more effective and equitable response for the future.

The Next Pandemic

The Covid 19 pandemic was not the first to devastate the world and will not be the last.

The COVID-19 pandemic felt for many of us like it came out of the blue, but scientists have long been sounding the alarm about a potential pandemic from a corona virus.

We already had warnings with the SARS and MERS outbreaks, both caused by corona viruses, and both spilled over from animals into humans. Given the way people continue to encroach on animal habitats, trade wildlife and eat bush meat, it is increasingly likely that zoonotic diseases that come from animals will cause future pandemics.

This already happens more often than you might think. Since the 1940s more than 330 emerging infectious diseases have been identified, of which 60% were zoonotic. And when a new infectious disease does emerge, human migration, population growth, rapid global travel, climate change urbanisation and dense urban slums can all hasten its spread. Given that more people are living in closer proximity to each other than ever before and that

normally more than a billion people cross international borders each year, it has never been easier for outbreaks to escalate and spread globally.

With the current pandemic, research carried out in response to previous corona virus outbreaks and developments in vaccine technologies gave us a head-start that meant that COVID-19 vaccines could be developed rapidly. Even so, at the outset we had limited national systems for case detection and tracking of epidemic spread. The complete lack of treatments or existing vaccines meant that in the year that it took to develop vaccines, millions lost their lives to COVID-19.

R&D tends to focus on immediate threats, and often on drugs, vaccines or diagnostics that are most profitable, which explains why many diseases identified by World Health Organization as having a high potential to cause future pandemics are currently being neglected. Many of these threats affect low- and middle-income countries and have little or no research and development ongoing. This is dangerous, and means that if any of these diseases turn pandemic, we could once again be caught off guard. Millions of lives could be lost.

Future Potential Pandemics?

Nipah virus?

Ebola?

Chikungunya?

H5N1 and H7N9 influenza?

Yellow fever?

Marburg?

Lassa fever?

Crimean-Congo Haemorrhagic Fever?

Hantavirus?

CONCLUSION

We need to recognize the close interactions between health and wellbeing of animals, humans and the environment.

COVID-19 pandemic and future pandemics are likely to emerge from ecological processes such as climate change, loss of biodiversity, anthropogenic social processes (e.g. corporate interests, culture and globalization) and world population growth. Intervention would therefore require modifications or dampening these generators

5. Laboratory Diagnosis of COVID-19

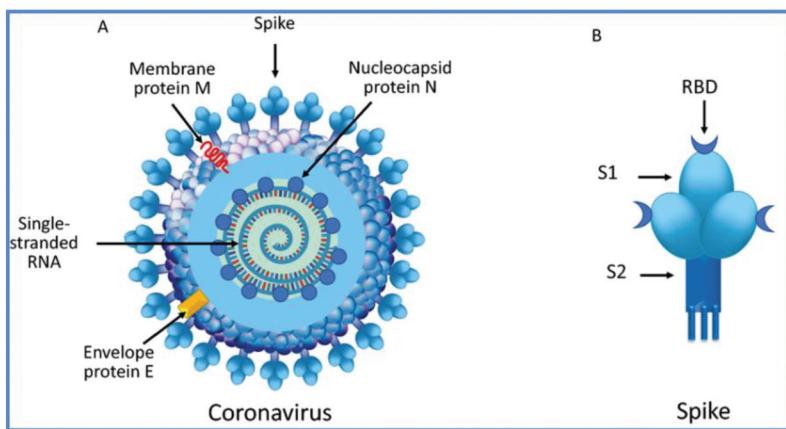


Fig 1: Structure of the SARS-CoV-2 Virus

A) Schematic representation of SARS-CoV-2 virus structure and the positions of the different proteins- Spike(S), Envelope(E), Membrane (M), Nucleocapsid (N) and single stranded RNA.

B) Schematic representation of the Spike glycoprotein showing the S1 and S2 segments and the Receptor Binding domain(RBD) which binds to the Angiotensin convertase enzyme-2 (ACE2) receptors on Human cells and facilitates entry of the virus.

Fig 4: Basic principle of PCR: Amplification of DNA occurs in 3 repeating steps-
1.denaturation, 2.annealing and 3.elongation.

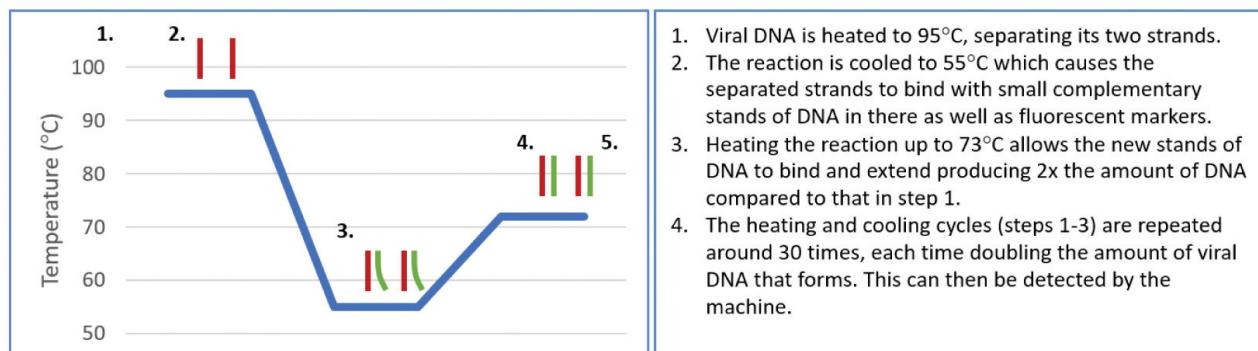
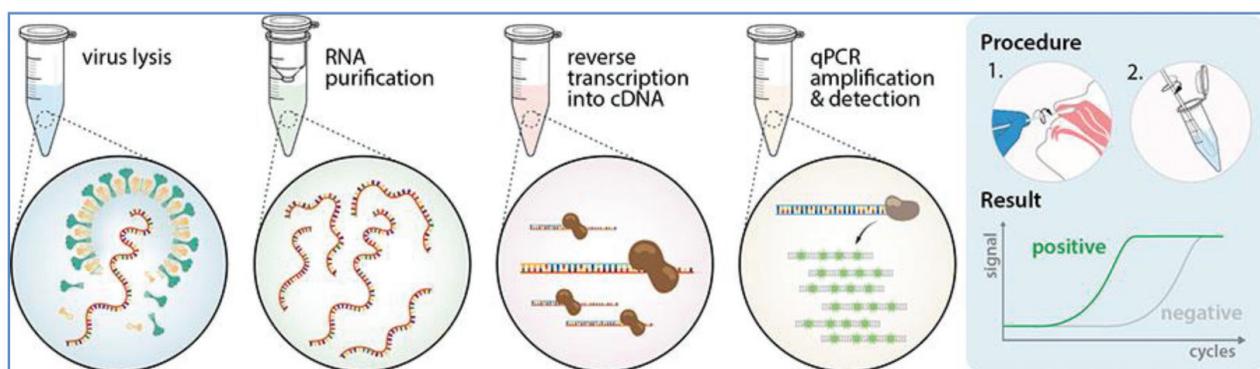


Fig.5 Basic Principle of Real time Real time RT-PCR for the diagnosis of COVID-19



7. Imaging in COVID-19

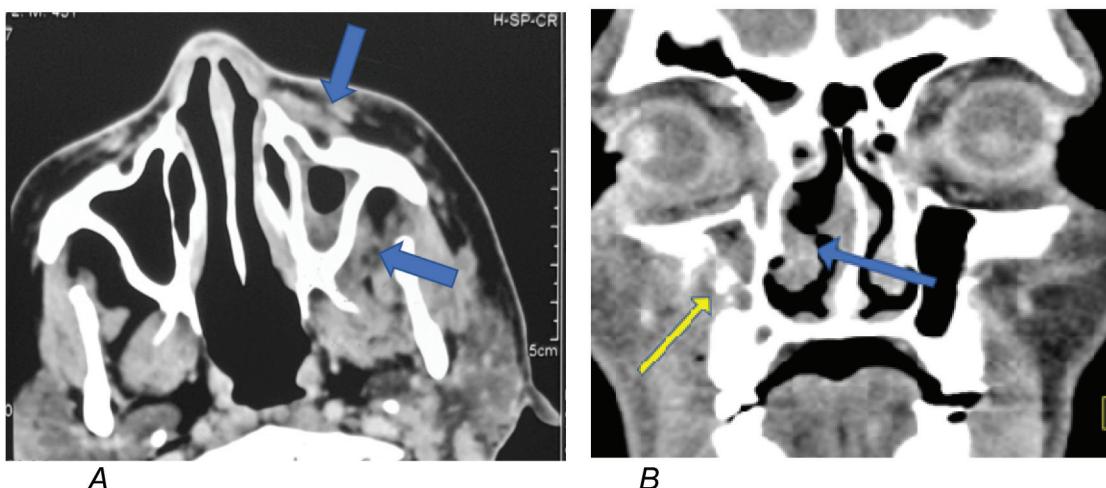


FIG 7. Imaging finding in acute invasive fungal rhinosinusitis: A: Axial CT shows left maxillary sinus mucosal thickening with peri-antral fat stranding without intervening bone destruction in a case of AIFRS. Note the retroantral fat plane infiltration is also in proximity to pterygomaxillary fissure and pterygopalatine fossa. B: Coronal CT shows ulcerated mucosal thickening in right nasal cavity (blue arrow) and maxillary sinus mucosal thickening with bone destruction (yellow arrow) in a case of AIFRS

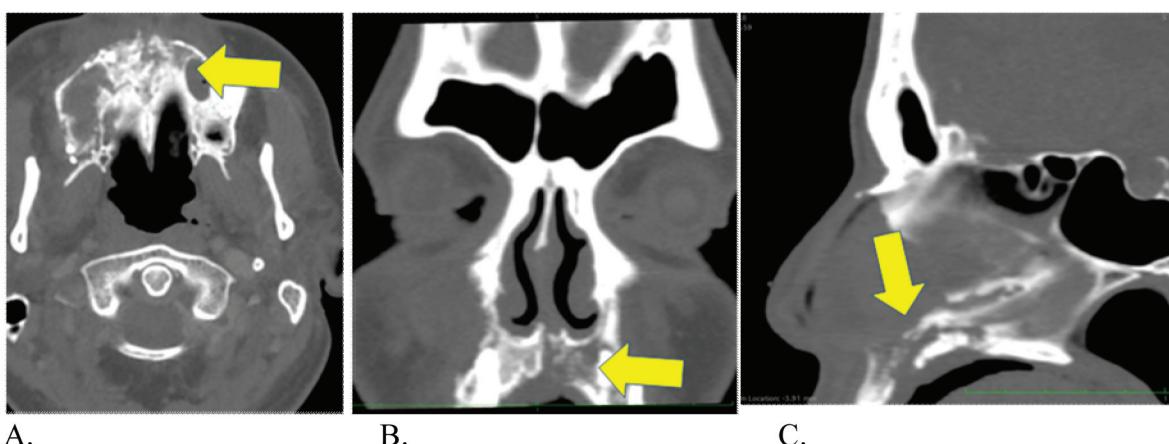


Fig 8. Bone infiltration by Mucormycosis. A-Axial CT shows erosion of floor of left maxillary sinus with involvement of hard palate; the erosion and destruction of hard palate can be Seen on coronal and sagittal reconstructed MDCT images (B&C)

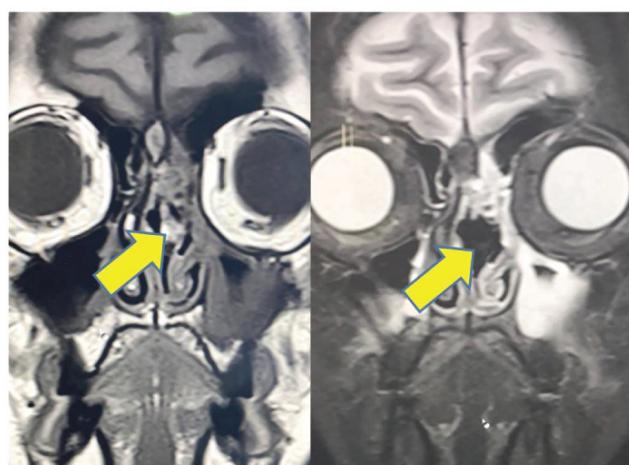


Fig 9. Turbinate Mucormycosis. Coronal T1 and T2FS MRI: focal high signal at left middle turbinate on T1W (arrow); the same area appears low signal on the T2FS MRI (arrow. Inflammatory changes at ethmoid and maxillary sinuses.

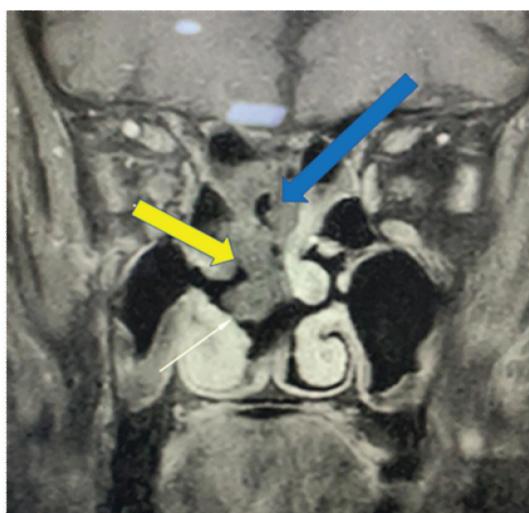


Fig 10. Mucormycosis: Sino nasal disease. Post contrast T1FS in a different patient: the right middle turbinate and nasal septum show no significant enhancement - 'black turbinate sign'; note the normal enhancement of mucosa over both inferior and left middle turbinate. Further inflammatory changes with poor enhancement noted at right ethmoid sinus and both maxillary sinuses.

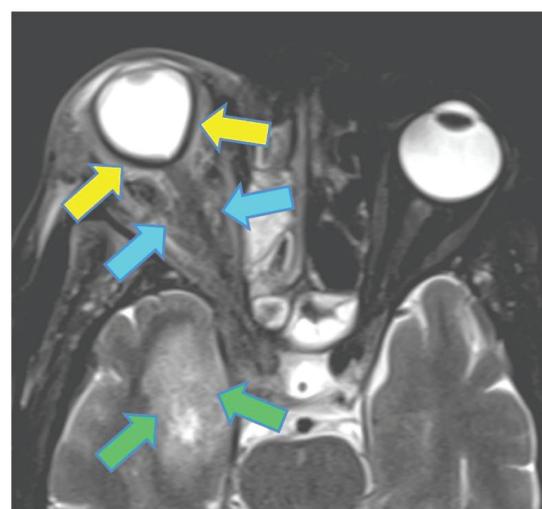


Fig 11: Mucormycosis - orbital, sinonasal and intracranial disease: T2FS axial image. Extensive fat stranding at intra and extra conal fat planes (blue arrow) with muscle edema resulting in distortion of globe which is shaped like a 'guitar pick' (yellow arrow) with proptosis. Note the cerebritis with possible early abscess formation at right temporal lobe (green arrow). Inflammatory changes at right ethmoid and sphenoid

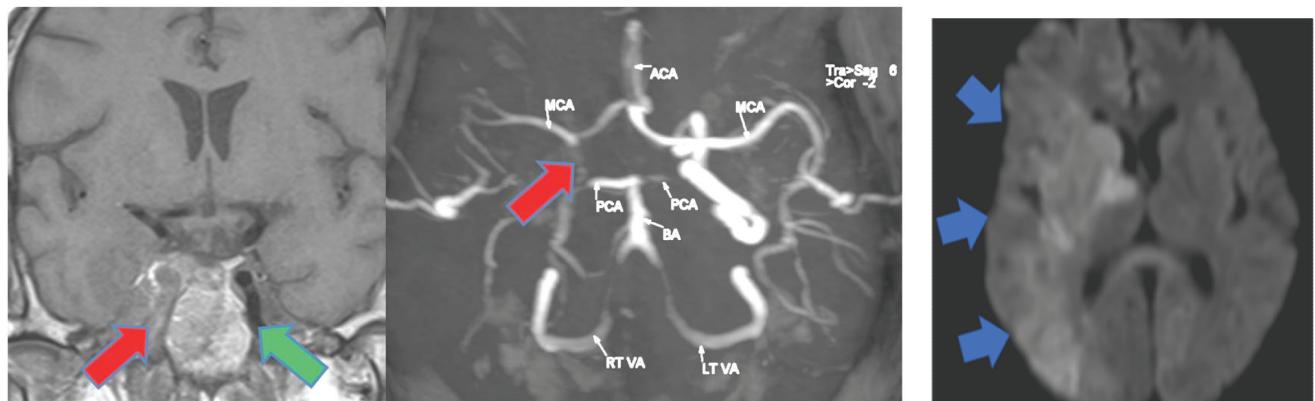


Fig 12. Right ICA occlusion: T1W coronal image show no flow void at right ICA at precavernous/cavernous segment (Red arrow); compare with normal left side. MR angiography show no flow signal at right ICA (Red arrow). Note the extensive right MCA territory infarct at right brain on DWI images (blue arrows).

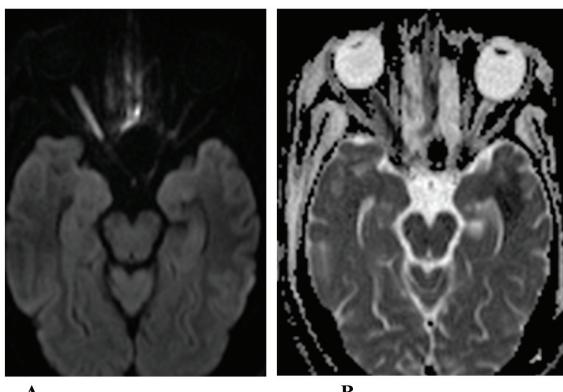


Fig 13. Optic nerve ischemia in a post Covid patient: A&B: Axial DWI and ADC map shows diffusion restriction in right optic nerve indicating infarction.

13. Antivirals for treating CoVID-19

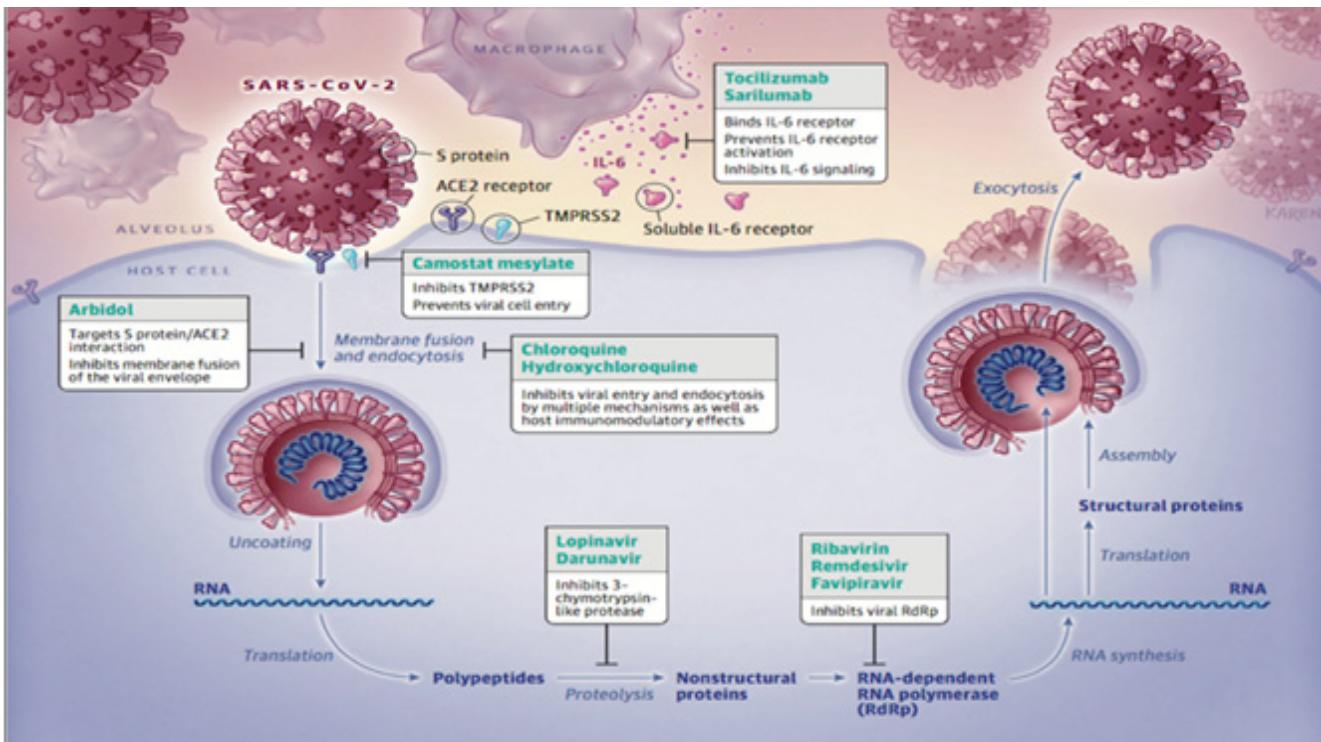


Figure 1 : Schematic Represents Virus-induced Host Immune Response And Viral Processing Within Target Cells.processed Tar. Gets Of Select Repurposed And Investigational Products Are Noted (JAMA)

21. COVID Vaccinology

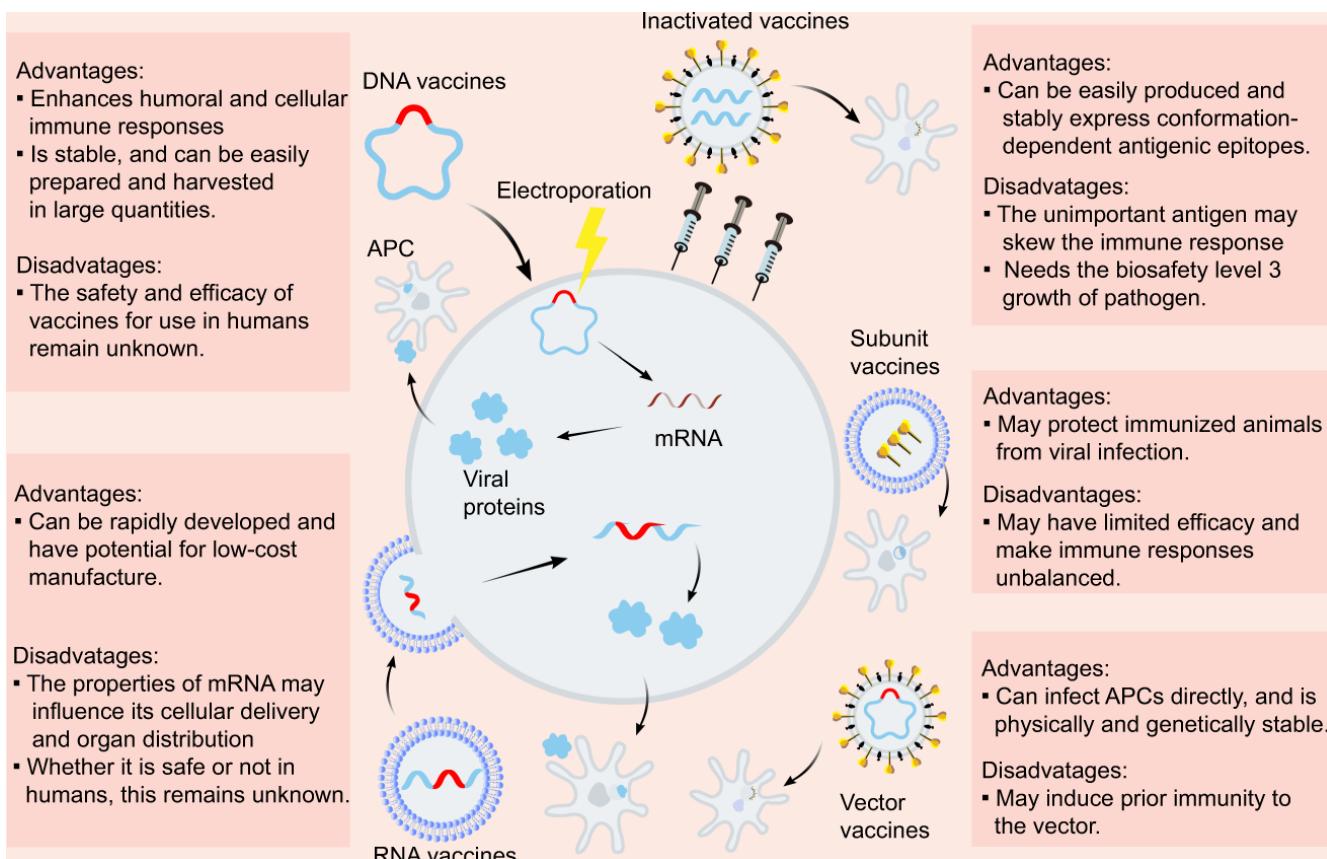
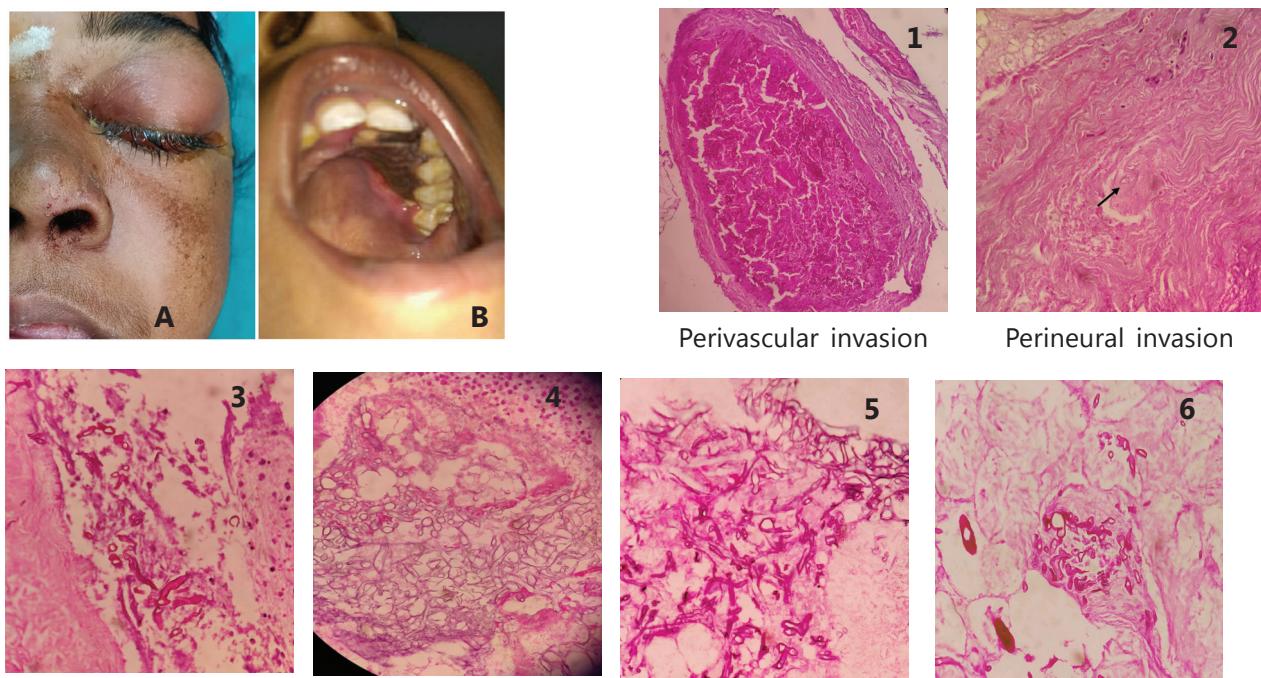


Figure 2 : Overview of the diverse types of vaccines, and their potential advantages and disadvantages.⁸
Ref: *Sig Transduct Target Ther* 5, 237 (2020)

31. COVID-19 and Mucormycosis



Broad aseptate hyphae with obtuse angle branching

A & B Courtesy - Dr. Devaraja K, Kasturba Hospital, Manipal.

1 to 6 : Courtesy - Dr Swati Sharma, Dr Nikitha Valerina Kairanna and Dr Megha Murali, KMC, Manipal

32. Nephrology and COVID-19

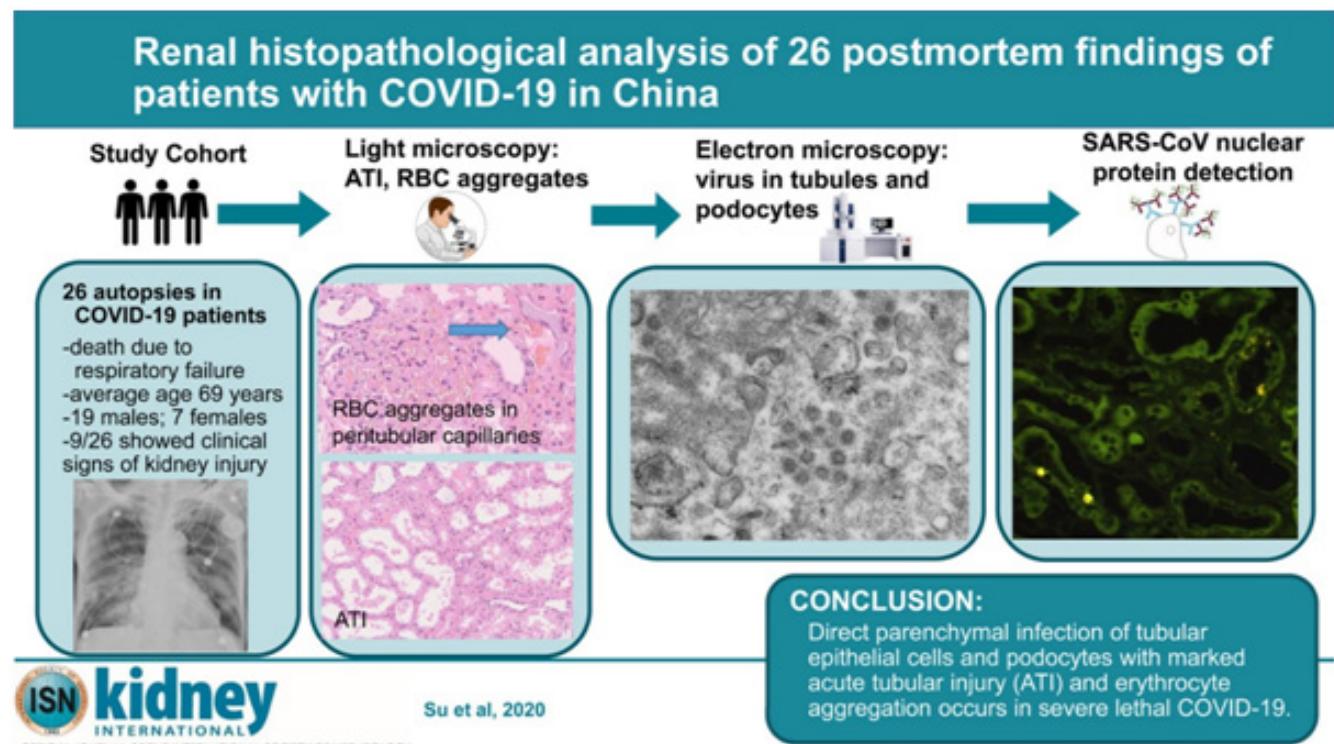


Figure 4 Renal Histology in Covid¹⁴

35. Covid and the Eye

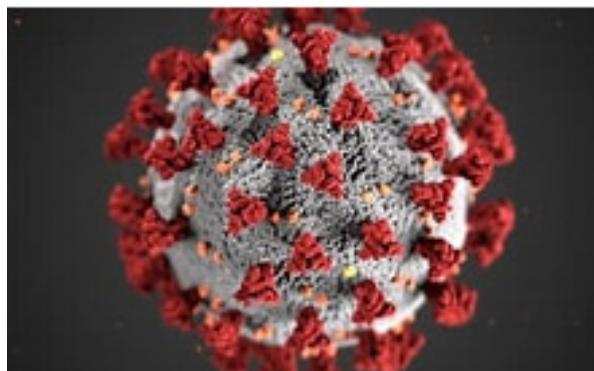


Figure 1 : This illustration, created at the Centres for Disease Control and Prevention reveals ultrastructural morphology exhibited by Coronavirus showing the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding the virion when viewed electron microscopically.

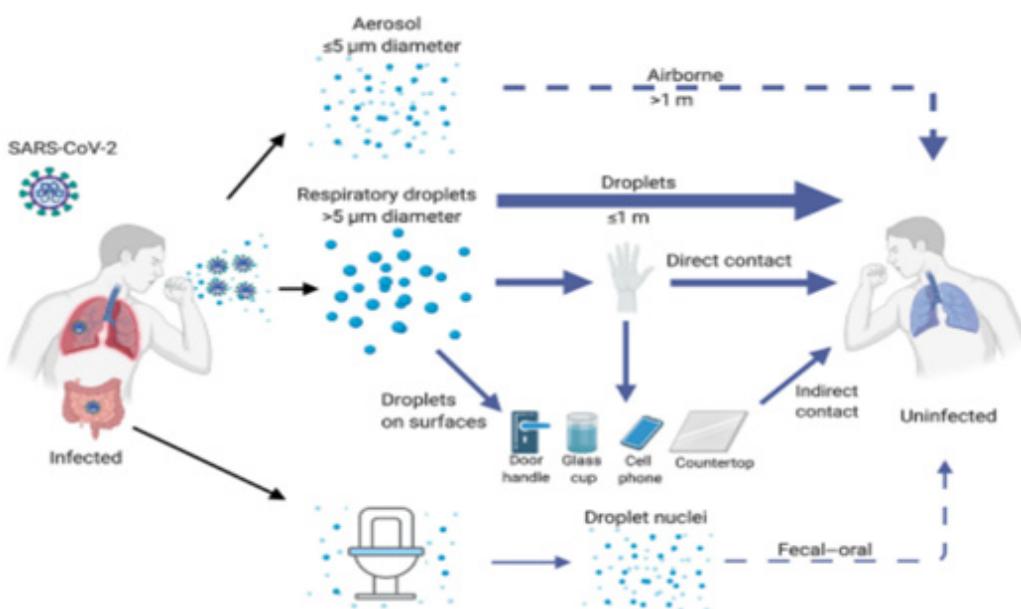


Figure 2 : Proposed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Transmission Routes



Figure 3. Follicular conjunctivitis in a COVID-19 positive patient



Figure 4 (a) - CRVO

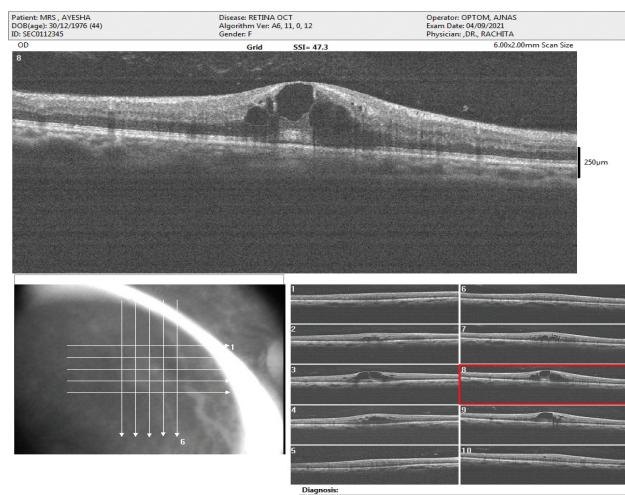


Figure 4 (b) - CRVO OCT



Figure 5 (a) - CSCR

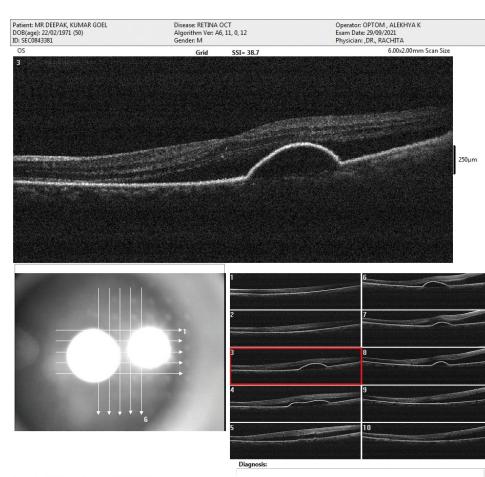


Figure 5 (b) - CSCR



Figure 6 - 6th Cranial nerve palsy



Figure 7 - Dacryoadenitis



Figure 8 - Rhino-orbito-cerebral mucormycosis

36. Surgical Issues in COVID-19: Maintenance of safety and regulation in surgical care, the effect on patients, education, career and research and the role of surgery in COVID care



Figure 1: Acute ischemia of right hand showing pale palm with cyanosis of finger tips.



Figure 2: Sagittal section of a CT Aortogram showing Aortic mural thrombus attached to the descending thoracic aorta and thrombotic occlusion of the celiac artery in a patient who presented with acute abdominal pain due to splenic infarcts 4 months after contracting COVID-19



Figure 3: Venous gangrene of the left leg due to extensive DVT up till the ilio-femoral segment



Figure 4: Preoperative image of patient with orbital complications.



Figure 5: Postoperative image with improvement in orbital complications



Figure 6: Preoperative CT PNS.



IMA NATIONAL HEALTH SCHEME

Approved in Central Council 2014
Started in 2015



With the Aim to provide financial assistance to its member and his/her spouse, children and parents in the event of hospitalization for treatment, diagnosis and management of diseases

Benefits of the Scheme : Treatment cost above Rs. 5000/- to 2Lakhs will be covered per year -It will be increased to 2.5 to 3 lakhs as membership grows. Members and his dependents with pre-existing Diseases like Cancer, Cardiac, Life style diseases or any other Serious diseases are allowed to join this Scheme.

This provision makes IMA National Health Scheme unique from other schemes.

Fee Structure at the time of joining (First Year)

Payment Chart of NHS according to age group

Payment chart at the Time of Joining

Age	AF	AMS	AFAC	Total
Less than 25yrs	1000	500	2500	4000
Above25 below35yrs	1000	500	3000	4500
35 to below 45yrs	1250	500	3000	4750
45yrs to 55yrs	1750	500	3000	5250
55 to below 60yrs	5000	500	5000	10500
60 to below 65yrs	7000	500	7000	14500
65yrs to below70yrs	8000	500	8000	16,500
70 to 80 yrs	10,000	500	10,000	20,500

Admission Fee is onetime Payment AMS & AFAC have to be paid every Year

Payment chart for renewal from 2nd Year onwards

Age	AF	AMS	AFAC	Total
Less than 25yrs	nil	500	2500	3000
Above25 below 35yrs	nil	500	3000	3500
35 to below 45yrs	nil	500	3000	3500
45yrs to below 55yrs	nil	500	3000	3500
55 to below 60yrs	nil	500	5000	5500
60 to below 65yrs	nil	500	7000	7500
65yrs to below 70yrs	nil	500	8000	8,500
70 to 80 yrs	nil	500	10,000	10,500

AMS &AFAC have to be paid every Year

Salient Features of IMA National Health Scheme (NHS)

1. In IMA NHS there is no escalation of annual premium amount even if the age progresses to the next slab for that particular insured amount. For example a person joining the scheme at the age of 25 years will be paying the same amount of Rs.3500/- till 55yrs as renewal fee per annum for an upper limit of 2 lakhs benefit.
2. Scrutinizing committee will examine the genuineness of the claim. 75% of the Total bill will be reimbursed to a maximum of 2 lakhs. Will be increased to 2.5-3lakhs
3. Allowed to join other insurance schemes and State Health Schemes. Total 3+2= 5 Lakhs benefits State HS+ National H.S
4. All pre-existing diseases are covered including Cancer and Organ Transplant
5. No medical screening test required for joining IMA National Health Scheme.
6. Member can join till the age of 80 years. It is the only Scheme which allows the IMA member and his family to join above the age of 65yrs .For all other schemes age limit is restricted to 65 yrs as upper limit
7. Immediate relatives of life members of IMA can also join.
8. Original bills are returned at request with Self addressed cover with stamp, and hence can be utilised for other insurance schemes for claim.
9. More than insurance companies, IMA NHS exist for the medical Fraternity and its family to provide financial help at the time of hospitalization.
10. Rs.50/- is eligible per member enrolled as promotional fee to local Branch or State branch or individual who promote the enrollment of NHS

Website : www.imanhs.com

It is an Additional Health Financial Scheme

Man by Professionals for profession. No Bureaucracy, so member friendly



INDIAN MEDICAL ASSOCIATION NATIONAL FAMILY WELFARE SCHEME

A SCHEME EXCLUSIVELY FOR THE SCHEME MEMBER'S FAMILY
AFTER DEATH & FOR THE DISABLED, END STAGE DISEASED
AND UNFIT TO PRACTICE

Admission Fee :

Age	Admission Fee	1 st Annual Subscription Fee	Total Admission Fee
Below 30 Yrs	3,000	500	3,500
31-40 yrs	5,000	500	5,500
41-50 yrs	7,000	500	7,500
51-60 yrs	10,000	500	10,500
61-65yrs	20,000	500	20,500

Payment Mode :

DD/Cheque in favour of "**IMA National Family Welfare Scheme**" Payable at Nedumangad, Thiruvananthapuram District.

Annual Subscription:

Every year member should pay Rs.500 as annual subscription for 25 years. After that member will become Honorary Member and become eligible for all rights.

One Time Payment :

By paying Rs.4,00,000 as Non refundable deposit the member will become life Member and become eligible for all rights and no need to pay other payments.

Member Benefits or Rights:

- On the event of demise of a member : Fraternity Contribution RS.300/- (200/- to Fraternity Contribution & Rs.100/- to corpus fund) on the event of demise of any member (To a maximum of 50 deaths per year over which the Fraternity Contribution will be taken from the corpus fund)
- Disabled or incapacitated Practitioner member will get a benefit from the Corpus Fund which will be judicially decided by the Management Committee.

LOCK IN PERIOD

If the Age joining the scheme is below 50 years, the lock in period is 2 years.

If the Age of joining the scheme is above 50 years, the lock period is 3 years.

FOR MORE DETAILS:

Log on to www.ima-india.org IMA National Family Welfare Scheme.