

# JAAPI

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“Wherever the art  
of medicine is loved,  
there is also a  
love of humanity.”  
- Hippocrates

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This Summer Issue of JAAPI is Dedicated to  
**Elizabeth H. Blackburn, Ph.D.**  
Nobel Prize in Medicine or Physiology 2009



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**Discovered the molecular structure of telomeres, and co-discovered the enzyme telomerase, essential piece in the puzzle of cellular division and DNA replication. Her research offered hope for cancer treatment, clues to the mystery of ageing and even biological links between life circumstance and lifespan.**

[www.nobelprize.org](http://www.nobelprize.org)

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## Pioneers in Medicine and Healthcare

### Elizabeth H. Blackburn, Ph.D.

#### Winner: 2009 Nobel Prize in Physiology or Medicine

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*My point and plea today, is to forge a farsighted agenda to develop a more global way of thinking, even a plan for science, to serve our shared future. Not just as individual national communities with narrow interests and viewpoints, and not just for the next few years, but broadly and for the next decades. – Elizabeth Blackburn, Ph.D. at the 68<sup>th</sup> Lindau Nobel Laureate Meeting held in Lindau, Germany, June 2018.*

In 2009, the Nobel Assembly at Karolinska Institute awarded the Nobel Prize in Physiology or Medicine jointly to Elizabeth Blackburn, Carol Greider, and Jack Szostak for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase. According to the Nobel Assembly: *An organism's genes are stored within DNA molecules, which are found in chromosomes inside its cells' nuclei. When a cell divides, it is important that its chromosomes are copied in full, and that they are not damaged. At each end of a chromosome lies a cap or telomere, as it is known, which protects it. In 1980, Elizabeth Blackburn discovered that telomeres have a particular DNA. In 1982, together with Jack Szostak, she further proved that this DNA prevents chromosomes from being broken down. Blackburn and Carol Greider discovered the enzyme telomerase, which produces the telomeres' DNA, in 1984 (1).*

The discovery of telomere and telomerase has broad and significant impact in the medical field, especially in cancer, aging, and certain inherited diseases affecting bone marrow, lung, and skin. Insufficient cell division in hematopoietic stem cells in bone marrow may result in anemia. Cancer cells, which divide infinitely express higher levels (80-90%) of telomerase enzyme to preserve their telomeres. Based on these findings, therapeutic strategies are in development to target telomerase activity using vaccines that specifically act on cancer cells with higher telomerase activity. Such vaccines should be effective against all types of cancers. Thus, the seminal discoveries made by Drs. Blackburn, Szostak, and Greider on the structure and activities of telomere and telomerase have far reaching benefits in medicine and healthcare.

True to the words of the Nobel Academy that Elizabeth Blackburn has evolved from a self-described "lab rat" to an explorer in the realms of health and public policy, she stood unique among the contemporary Nobel Laureates in Physiology or Medicine. Dr. Blackburn served as President of the Salk Institute for Biological Studies, President of the American Association for Cancer Research, President of the American Society for Cell Biology, Member of the Institute of Medicine and Royal Society of London, and Foreign Associate of the National Academy of Sciences. In addition to the Nobel Prize, Dr. Blackburn received every major award which scientists covet, such as Lasker, Gruber and Gairdner prizes. Dr. Blackburn has been active in shaping science policy and ethics. She has been a Member of the President's Council of Bioethics, and advisory committee to the President of the United States. Dr. Blackburn was also named as the most influential people in the world by Time 100 in 2007.

Dr. Blackburn was born in Hobart, a small city in Tasmania, Australia, in a family of doctors and scientists. Both her parents were physicians, her grandfather and great-grandfather were geologists. Inspired by the life and work of Marie Curie, Dr. Blackburn chose to become a scientist. After graduating with bachelor's and master's degrees in Biochemistry from the University of Melbourne, she did Ph.D. in molecular biology from the University of Cambridge in England, and then postdoctoral research at the Yale University. Dr. Blackburn worked as faculty at the University of California, Berkeley and then at the University of California, San Francisco. Currently, she is a Distinguished Professor Emeritus at the Salk Institute, La Jolla, California.

**Compiled by: Bellamkonda K. Kishore, M.D.**

## From the Editorial Desk

### Peer-Review Process: The Pillar of Evidence-Based Medicine

Suresh Karne, M.D., Ph.D.

Associate Editor-in-Chief of JAAPI

*A scientist cannot do anything that is not checked and rechecked by scientists of this network before it is accepted. - Sune Bergström, Swedish Biochemist*

September 19-23, 2022, was observed as Peer Review Week globally, celebrating the pivotal role peer review played in maintaining quality of research and thus supporting the Evidence-based Medicine (EBM) as one of the two pillars, the other pillar being Randomized Control Trials (RCT). I would like to take this opportunity to describe how peer-reviewed journals, such as the JAAPI, process articles for publication.

For any scientific journal to succeed and have real impact and credibility, it is important to follow a strict protocol for accepting articles for publication and to maintain an autonomous process free from external or internal influence or pressures. We are happy to report that JAAPI, with unconditional support from AAPI Leadership right from the beginning, and dedicated Editorial Board Members, has been able to achieve this benchmark and sustain it uninterrupted. This in turn resulted in very favorable ratings for standards of JAAPI by peers from different places within a span of one year. On behalf of the Editorial Board, I want to thank all the authors who have contributed articles, and reviewers who have supported the journal. JAAPI is now well poised to successfully seek registration with the National Medical Library, leading to citations in the PubMed for the articles published in JAAPI.

JAAPI welcomes original clinical or basic science research articles, review articles and case reports, perspectives, commentaries, and others. JAAPI publishes articles from researchers from all over the world, without national or ethnic barriers. JAAPI encourages researchers from all specialties to publish, which is evident in each of the issues of JAAPI published so far. Authors and reviewers of the articles, as well as Guest Editors need not be members of AAPI. But regular Editorial Board Members need to be members of AAPI and subscribe to the vision, mission, and core values of AAPI and thus are accountable to AAPI Leadership.

When an article is submitted, it is first subjected to quality control checks, for originality of the article, ensuring no violation of copyright issues that may lead to accusation of plagiarism, which is a serious matter in the world of publication. This is achieved using plagiarism detection software, which compares the text of the submitted articles against billions of articles on the web within a couple of minutes or less. Ensuring no copyright violation also requires that figures, schemes and tables are original, or permission is obtained through Copyright Clearance Center by the authors to reproduce. Clinical studies and case reports need approval of the Institutional Review Board (IRB) and informed consent of the patient(s). Studies involving laboratory animals require approval of the Institutional Animal Care and Use Committee (IACUC). All authors should sign a Consent to Submit Form, which ensures that all authors have read the paper and approved its content as well as the sequence of authorship and affiliations. Due to increased number of retractions of papers for various reasons, author consent and approval is no more an academic, but a legal issue, especially if the study involves federal or taxpayer's dollars, which includes salaries of the authors as well. After the article successfully passes through quality control stage, it is sent for evaluation by experts in the field, the so called "peer reviewers." This is the key aspect that maintains quality of the journal. The peer-reviewers need to sign no Conflict-of-Interest Form declaring that they do not have professional or personal conflict of interest with the authors or their institutes which may potentially result in biased (either positive or negative) review outcome. The reviewers submit their critical analysis and opinion about the article in writing using Reviewer's Comments to Authors Form, which has several sections to address every aspect of the article. In parallel, the reviewers submit their Confidential Comments regarding suitability of the article for publication to the editor using a separate form. It should be noted that peer-review is not

correcting or proofreading the manuscript to improve its quality of presentation. Peer review is critical analysis of the contents using specific criteria. So, peer reviewers need knowledge in the field of the article, should have strong interest in scholarly journals and experience in reviewing, critically analyzing and commenting on the contents of the articles. Peer reviewers should be able to express their comments clearly in good English so that editors and authors can understand them. More importantly, peer reviewers who commit should have enough time to complete the review process in a timely manner. The reviewers may recommend minor or major revisions or rejection of the manuscript. If the recommendations are minor or major, authors are asked to address the concerns raised by the reviewers and submit a revised version of their article. If a rejection is recommended, the Editor-in-Chief or Associate Editors-in-Chief gives an opportunity to the authors to address issues raised by the reviewers for rejection as well as the concerns of the editor, if any and make a *de novo* submission of the article for a fresh review cycle. It is up to the authors to either avail that opportunity and make a *de novo* submission or ignore the request. Thus, the goal of JAAPI is to encourage authors to improve the quality of their articles, not simply rejecting them.

Peer review process is relatively new, less than 100 years old as compared to the history of modern science and medicine (1). Many scientific societies reviewed (mostly by editors) and published articles without the help of any external reviewers. In the 1950s-60s, many journals including *Nature*, *Science*, *British Medical Journal*, asked experts with no conflict of interests to the authors of the paper to review prior to publication. *Lancet* employed external peer-reviewers from 1970s only.

Peer-review process has been both praised and criticized by renowned researchers. Some researchers (including Albert Einstein) have expressed the opinion that the editor should review and publish the paper without external reviewers (as fellow researchers have the advantage of knowing about a topic before everyone and that this is an advantage that should not be offered to a select few). Others have suggested that peer-review is vital to have as it offers referee before the article is available to “public-at-large (2-4).

It has always been the policy that the editorial board and the publisher are ultimately responsible for the publication; but relying on external experts to “critically assess” the articles prior to publication. It has now become gold standard for scientific publications. Few journals disclose the reviewers to authors during the review process, others follow one-sided blind process during review process by which the reviewers know the identity of the authors, but the authors are blind to the identity of the reviewers. Double blinding is not possible all the time, as one can easily guess the identity of the authors based on the nature of the work, and references to their previous work, which is very common. A few journals, like JAAPI disclose the identity of the reviewers when the paper is published, while majority of journals keep the identity of reviewers confidential forever. The model followed by JAAPI has some advantages, as it gives due credit to the reviewers for their efforts. It also ensures fair review process without being unduly critical of the article.

Thus, the Editorial Board of JAAPI is committed to adhering to the highest standards of scientific publication, which elevates the stature of not only JAAPI, but also AAPI as a professional organization. In fact, AAPI is the first association of ethnic doctors in the United States that launched its own peer-reviewed journal. To the best of our knowledge, no other ethnic doctors’ association in the United States has its own peer-reviewed scientific journal.

We encourage all to support JAAPI by submitting articles and lending your expertise in reviewing the articles submitted for publication. JAAPI offers a unique platform for members of AAPI, YPS, and MSRF to publish their professional work.

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## Scope of the Journal & Instructions to Authors

**Vision and Mission:** JAAPI is a peer-reviewed medical and healthcare journal published by the AAPI. In line with the vision and mission of AAPI, JAAPI is dedicated to facilitating physicians to excel in patient care, teaching, and research, and thus pursue their aspirations in professional and community affairs. JAAPI is open to contributions from physicians and scientists of all backgrounds and from all over the world. Membership in AAPI is not mandatory for prospective authors.

**Scope of JAAPI:** JAAPI publishes a variety of articles, such as original research articles, clinical studies, reviews, perspectives, commentaries, case studies etc., covering all aspects of medical sciences, clinical specialties, and healthcare, including epidemiology, and policy, regulatory and legislative issues. Articles submitted to the JAAPI must be original and should not have been published or under consideration for publication elsewhere, except in abstract form in proceedings of conferences or meetings. Only manuscripts that meet professional and scientific standards will be accepted for publication. Review process is single fold blinded on the authors' side. But after acceptance of papers, the names of the handling Editors and Reviewers will be published on the front page of the article. This new trend started by some European journals is gaining momentum as it gives due credit to the Editors and Reviewers and ensures fair review process.

**Publication Model:** JAAPI is published as completely Open Access in electronic form (PDF). These will be archived in AAPI website (<https://www.aapiusa.org/jaapi/>), and the link to URL for each issue will be emailed to AAPI Members when it is published. A few hard copies will be printed for promotional purposes and for displaying at AAPI Conventions and other professional meetings or for distributing to libraries or dignitaries. There will be no submission fee or publication charges to the authors. Although materials published are copyrighted by the AAPI, others can cite or reproduce figures, schemes and pictures published in JAAPI without paying fee, but by giving due credit to JAAPI. This does not apply for materials reproduced in JAAPI from other journals, which are copyrighted by the original publisher.

**Registration and Indexing:** After meeting the required criteria, JAAPI will be eligible for applying for registration with MEDLINE. If successfully registered, JAAPI will be indexed in the PubMed operated by the National Library of Medicine. JAAPI will also be registered for indexing in other major bibliographic databases, such as SCOPUS (managed by Elsevier), EMBASE (Excerpta Medica Database), DOAJ (Directory of Open Access Journals), Ovid (Walter Kluwer Ovid Database) and BioMed Central Database. JAAPI is in the process of securing DOI (Digital Object Identification) numbers for its published articles, which will result in articles appearing in Google Scholar.

**Editorial Board:** The Editorial Board of JAAPI consists of one Editor-in-Chief, two Associate Editors-in-Chief, two Editorial Advisors, several Deputy Editors and Guest Editors covering different areas of medicine and health care, Editorial Board Members (Internal Reviewers). They will be aided by External Reviewers. The Editor-in-Chief and Associate Editors-in-Chief oversee the overall peer-review process, assign articles to Deputy Editors or Guest Editors, and accept or reject articles after peer-review. They also preview articles prior to peer-review process and determine whether they can be subjected peer-review process. The Editorial Advisors to provide advice to ensure good performance and stability of JAAPI and to help in logistics, administrative and fiscal issues. The Deputy Editors and Guest Editors will handle review process of submitted papers assigned to them with the assistance of internal (Editorial Board Members) and external reviewers. AAPI membership is required for all Editorial Board Members, except Guest Editors, who are expected to promote the vision and mission of AAPI through JAAPI.

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- **Original Research Articles:** These describe original scientific or clinical research conducted on in vitro or animal models or human subjects after obtaining approval by the concerned institutional animal care and use committees or human subjects research review boards. The research should comply with the guidelines and regulations of US Public Health Service. The original research articles can be 3,000 to 4,000 words in length, excluding title page, abstract, legends and references. Maximum 7 figures or tables are allowed. Additional figures or tables need to be justifiable for the article. Supplemental Information (SI) containing data and text, such as methods, are allowed for deposition.
- **Review Articles:** The review articles can address any contemporary issue in medical or clinical sciences, or healthcare, including epidemiology, and policy, regulatory and legislative issues. The reviews should provide in depth analysis of the topics but should not be just presenting catalog of information. The review articles should be balanced and should cite literature without bias. The review articles can be 3,000 to 5,000 words, excluding title page, abstract, references, and legends. Not over 7 figures and tables combined. There is no limit on the number of references, but they should be recent and relevant ones. Review articles exceeding these limits will be considered if they are justifiable and provide
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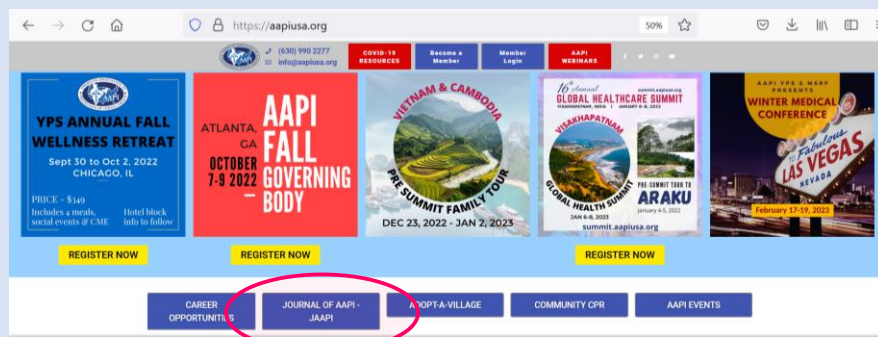
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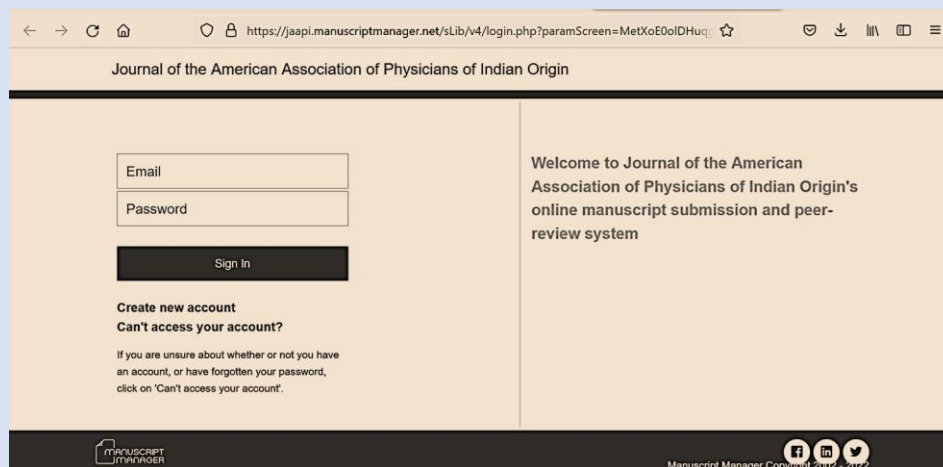
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To keep a paper trail of business correspondence, we encourage authors to communicate with Members of the Editorial Board in writing through the Manuscript Management System, rather than calling or texting them on cell phones. Besides, the Editorial Board Members may not have time to take phone calls during daytime due to their professional duties.

# **JAAPI Awards** **for the** **Best Research Articles** **by YPS/MSRF Members**

Starting from 2022, each year JAAPI will give 3 awards for the Best Original Research Articles submitted by **YPS/MSRF Members as the first authors** and accepted for publication in JAAPI after peer-review process.

The Awards include the following cash prizes and a citation on a plaque.

**Winner – One Award \$1,000**  
**Runners – Two Awards \$500 each**

Membership in YPS/MSRF is mandatory at the time of submission of the Original Research Articles.

A panel of judges drawn from the Editorial Board will decide the winners.

Only Original Research Articles are eligible for entry, not Reviews or Case Reports etc. The criteria and details of the process will be published in the JAAPI web page.

## Call for Articles on Asian American Healthcare Issues



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It has been well documented that Asian Americans, especially the South Asians, have higher prevalence of cardiovascular diseases and face higher cardiometabolic risk. This is attributed to several factors, including genetics. On May 10, 2022, the Newsroom of the American Heart Association pointed out that “one-size-fits all” is flawed for assessing cardiovascular diseases risk among Asian Americans. In view of the above, starting from Spring 2022 Edition, JAAPI has a section dedicated to **Asian American Healthcare Issues**. We welcome articles on all aspects of Asian American or South Asian healthcare under this section.



## In Depth Review

# A Pathophysiologic Approach to COVID-19 Management and Current Status of Treatment and Recommendations

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**Abstract:** A multipronged approach is needed to manage COVID-19 illness, caused by SARS-CoV-2. It includes preventive strategies such as masking, physical distancing, sanitizing (CAB-COVID appropriate behavior) and vaccines & therapeutic strategies targeting (a) viral replication and (b) host immunological responses which injure the host due to collateral damage in containing the virus. An effective chemoprophylactic antiviral compound along with better clinical management by properly classifying the disease pathology and targeting therapy will lead to judicious use of medications to treat COVID-19. To achieve these goals several measures, include development of vaccines and repurposing of drugs to thwart viral replication and mitigate exuberant host immunological/inflammatory responses. Each measure has its own importance in addressing the threat posed by SARS-CoV-2 to the health of an individual and the community. This review describes relevant biology of the virus and key therapeutic interventions targeting SARS-CoV-2 entry, replication, and the inflammatory host immunological pathways, as part of prevention and treatment of COVID-19 to reduce pill burden for disease management as per recent recommendations. We are also reminded of the classical quote by Dr. David Ho an eminent virologist and AIDS researcher, "It is the Virus Stupid" and it must be contained with counter measures that target the virus and disease progression. Dr. David Ho's groundbreaking work to combat replicating HIV in patients with hard hitting antiretrovirals changed the death sentence of HIV/AIDS into a manageable problem and likewise provides us clue to effectively manage COVID-19.

**Keywords:** COVID-19, Clinical management, Immunity, Cytokine storm, Pill burden, Dr. David Ho

<b>List of Abbreviations Used</b>	
ACE	Angiotensin-converting Enzyme
ACE2	Angiotensin-Converting Enzyme 2
ACEIs	Angiotensin-converting Enzyme Inhibitors
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AECII	Alveolar Epithelial Type II Cells
ALI	Acute Lung Injury
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
CAB	COVID appropriate behavior
CoV	Coronaviruses
CP	Convalescent Plasma
CQ	Chloroquine
CRP	C-reactive Protein
DAMPs	Damage Associated Molecular Patterns
DIC	Disseminated Intravascular Coagulation
ECMO	Extracorporeal Membrane Oxygenation
EMPACTA	Evaluating Minority Patients with Actemra
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
HQC	hydroxychloroquine
IFN	Interferons IFN
IL-6	Interleukin 6
IMP	Importin
JAB	COVID-19 Vaccination
LDH	Lactate Dehydrogenase
mAbs	Human Monoclonal Antibodies
MAS	Macrophage Activation Syndrome
MERS	Middle East Respiratory Syndrome
Mil6r	Transmembrane IL-6 Receptors
NK	Natural Killer
NLRP3	Nucleotide-binding domain (NOD)-like Receptor Protein 3
NTD	N-terminal Domain
PAMPs	Pathogen Associated Molecular Patterns
PE	Pulmonary Embolism
PEP	Postexposure Prophylaxis
PrEP	Preexposure Prophylaxis
PRRs	Pattern-Recognition Receptors
RAAS	Renin-angiotensin-aldosterone System
RAS	Renin Angiotensin System Modulation
RBC	Red Blood Cell
RBD	Receptor Binding Domain
SARS	Severe Acute Respiratory Syndrome
TH1	T Helper 1

**Background:** Historically Coronaviruses (CoV) were discovered in chicken in 1930s and it was not until 1960s that they were reported to cause disease in humans. Two crucial years (2002, 2012) saw the emergence of zoonotic human CoVs-Severe Acute Respiratory Syndrome (SARS) CoV (Total cases 8098; mortality rate 9.5%) and Middle East Respiratory Syndrome (MERS) CoV (Total cases 2519 cases; mortality rate 34.4%) respectively (1-2). However, neither

escalated to pandemic proportions comparable in scale to SARS-CoV-2, causative agent for COVID-19 (3) declared as a Public Health emergency of international concern. Like its other family members SARS-CoV-2 is probably enzootic and jumped the species barrier in 2019 transmitting in humans with over 569 million people infected worldwide and over 6 million deaths as of July 2022, and still superseding the damage done by other human CoVs (4).

**Biology of a Quasi-species SARS-CoV-2:** SARS-CoV-2 high replication rate early in the infection cycle leads to emergence of viral quasi species and high genetic recombination to generate a population of heterogenous viral particles (5). These variants get notoriously designated either as Variants of Concern (VOC), Variants of Interest (VOI) or Variant of High Consequence (VOHC) based on their virulence and transmission dynamics that ensue public health interventions. Most intriguing aspect is that the continuous emergence of variants in the same individual spring forth evolution to more transmissible viral populations that may be virulent and potentially overcome immunity provided by wild type infection and existing vaccines. The recommendations of COVID-19 management are evolving based on our understanding of virus biology and host immune response. Hence, an ongoing human endeavor is to renew our line of COVID-19 management and viable treatment options.

COVID-19 infection manifests either as asymptomatic or symptomatic disease with illness ranging from mild, moderate, and severe that may necessitate hospitalization. Early symptoms include dry cough, fever or chills, shortness of breath, new loss of smell and/or taste, sore throat, congestion or runny nose, fatigue, muscle or body aches, headache, nausea or vomiting, and diarrhea while severe illness usually manifests after 7-10 days characterized by dyspnea and hypoxemia. The list of symptoms is evolving with the emergence of SARS-CoV-2 variants and disease sequelae christened as “Long COVID-19” with new/persisting symptoms in recovered individuals.

Severely ill patients show progressive respiratory failure with onset of bilateral infiltrates, severe hypoxemia and lung exudates fulfilling criteria of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Multi organ dysfunction and inflammation sets in with lymphopenia, thrombocytopenia, thromboembolic complications, coagulation disorders, acute kidney injury, cardiac arrhythmias, liver injury, disorders of the central and peripheral nervous system, hyperferritinemia with

elevated D-dimer, high levels of interleukin-6 (IL-6), LDH (Lactate dehydrogenase), and C-reactive protein (CRP). Disease severity induced by SARS-CoV-2 is attributed to a mix of factors that include virus inoculum, host age and underlying comorbidities like obesity, diabetes and existing heart ailments, respiratory diseases, cancer, and renal failure in affected host (5, 6). The uncertainty in disease presentation is not only due to infectivity of the virus but its consequent immune/inflammatory response to the viral replication in the host.

**Pathogenesis of SARS-CoV-2:** Pathogenesis of SARS-CoV-2 involves virus-host interactions, entry and egress from host cell, orchestration of innate and adaptive immune regulation (6, 7). After entry, virus proliferation is facilitated by taking over the host cellular machinery. The host's innate and adaptive immune system is activated to eliminate the virus. On entry of SARS-CoV-2, the first line of host defense by innate immune response is triggered. Macrophages and monocytes recruited to the site respond to infection, release cytokines and prime adaptive T and B cell immune responses (7). To mount the innate antiviral immune response (6), pattern-recognition receptors (PRRs) present on alveolar epithelial cells and alveolar macrophages detect the released pathogen-associated molecular patterns (PAMPs), such as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP, DNA and oligomers. Among PRRs, NLRP3 inflammasome activated by PAMPs or DAMPs catalyzes recruitment of caspases leading to activation of interleukins (6, 7). Recognition by innate immune cells lead to activation of downstream signaling cascade which results in the upregulation of expression of type I IFN and other pro-inflammatory cytokines and chemokines, caspases, IL-6, IFN-gamma, MCP1 and IP-10 into extracellular compartments of infected tissues. These cytokine responses are indicators of a T helper 1 (TH1) cell-polarized response (8).

The Th1 type immune response plays a dominant role in adaptive immunity to viral infections. Cytokine microenvironment generated by antigen presenting cells dictates the direction of T cell responses. Helper CD4 T cells orchestrate the overall adaptive response, while cytotoxic CD8 T cells essentially kill the viral infected cells and aid in viral clearance (9, 10). This initial response comprises the first line of defense against SARS-CoV-2 at the entry site. In majority of COVID-19 infected patients, activated immune cells can clear the infection, the immune/inflammatory response tapers off, and patients recover.

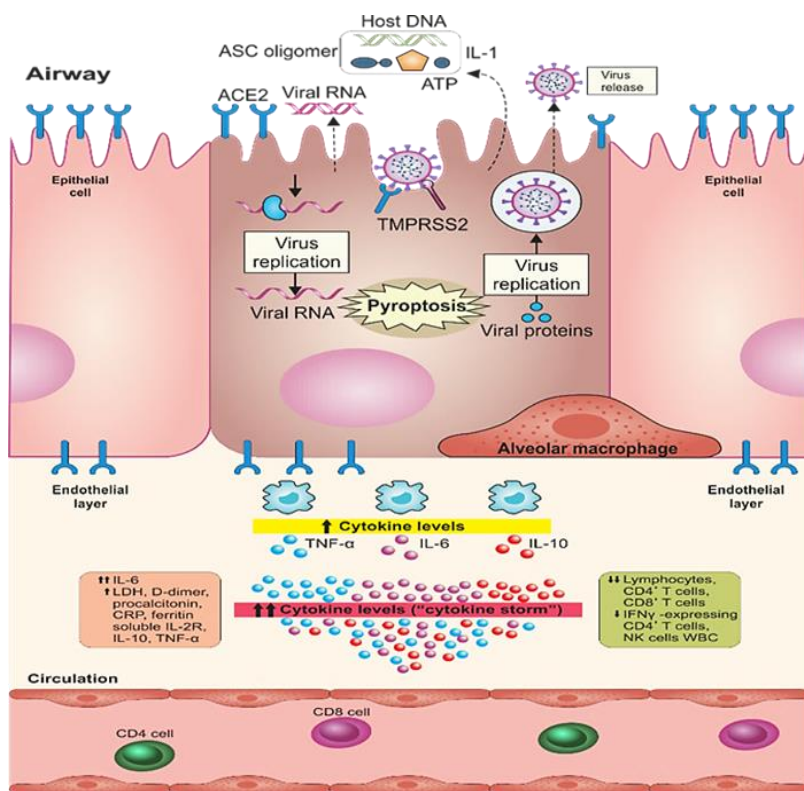
Interferons limit virus spread and play an immunomodulatory role to promote macrophage phago-cytosis of antigens and Natural Killer (NK) cells mediate restriction of infected target cells and modulate exuberant macrophage activation. The initial immune response is the key to containing disease severity as inappropriate dampening immune response early on can be treacherous. Regarding B-cell activation, total levels of IgG and IgM have been reported to be similar between severe and mild COVID-19 cases suggesting no major general impairment in B-cell activity; IgM response peaks around day 9 after disease onset and the switching to IgG by week two (6).

SARS-CoV-2 virus can circumvent host antiviral responses resulting in uncontrolled viral replication, which is an area of immense study. The sudden clinical worsening in severely affected hospitalized COVID-19 patients is driven by a unique pattern of immune dysfunction. The immunopathology of lung leading to ALI and ARDS results from overdrive of inflammatory responses or "cytokine storm" as witnessed by soaring levels of blood inflammatory markers and excessive unabated oxidation stress that results in the activation of the cytokine storm (Figure 1) (6-8). The advent of cytokine storm in COVID-19 infection is derived from our understanding of cytokine storm in other human coronavirus infections (11). High influx of pro-inflammatory factors leads to increased vascular permeability and entry of fluid and blood cells into the alveoli, resulting in dyspnea and in severe cases respiratory failure due to impaired oxygenation and alveolar gas exchange. Pro-inflammatory cytokines also lead to increase in von Willebrand factor aggregation into multimers in activated endothelial cells along with release of chemokines, clumping of platelets (thrombus formation) and activation of the complement cascade. Furthermore, myriad COVID-19 clinical manifestations and long-lasting sequelae involve Multisystem Inflammatory Syndrome (MIS) orchestrated either by inflammatory factors and/or deposition of immune complexes/ Ig mediated complement activation leading to vasculitis, acute kidney injury, myocarditis, involvement of Central Nervous System and Peripheral Nervous System with neurological manifestations and Kawasaki-like disease in children and adults with SARS-CoV-2 infection (12).

Like SARS-CoV, SARS-CoV-2 prefers binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2) to gain entry to the host cell (13, 14), although this may not be the receptor of choice in some variants. ACE-2 is proven to be present on vascular endothelial cells, the renal tubular

epithelium, Leydig cells in the testes, lung, kidney, and gastrointestinal tract and in some hematopoietic cells, (ACE2) express 83% of ACE2, hence the lung tissue is most susceptible to the virus (14). The N-terminal domain (NTD) of SARS-CoV-2 Spike (S) protein also engages with 9-*O*-acetylated sialic acid-containing receptors. The Receptor Binding Domain (RBD) recognizes ACE2 while the NTD binds a lipid raft rich in ganglioside at the cell surface; S glycoprotein priming by host serine protease-TMPRSS2 leads to viral fusion with the cell membrane (5, 14, 15). Widespread presence of ACE2 also explains the multi-organ involvement in SARS-CoV-2 as virus-receptor interaction modifies the local microenvironment of immune complexes in blood vessels and alveoli causing immune complex related endothelitis (12); Abundant ACE2 gene expression has been recently reported in subcutaneous and visceral adipose tissue compared to the

including monocytes and macrophages (13, 14). According to Zhao et al (2020) lung alveolar epithelial type II cells lung tissue (16). As per an experimental study, SARS-CoV-2 infection impaired insulin/IGF (Insulin-like Growth Factor) signaling in adipose tissue and several other organs (17). Obese patients with abundant adipose tissue are hence more susceptible to virus entry into cells and proliferation leading to multi organ involvement with severe COVID-19 disease (18). Also, affinity to human gut epithelium has long term implications in viral fecal-oral transmission of the virus and will impact its containment due to persistence in wastewater from households and treatment facilities (19). This indeed makes an interesting surveillance tool to detect presence of SARS-CoV-2 in wastewater samples as a surrogate marker to predict possible outbreaks.



**Figure 1: Pathophysiology of Cytokine Storm:** SARS-CoV-2 entry is facilitated by binding to ACE2 receptor. Since respiratory epithelial cells abundantly express ACE2 receptor they demonstrate high levels of damage caused by inflammasome induced pyroptosis. Acute lung injury and inflammation promotes neutrophil infiltration and further burst of cytokines. Patients with severe infection manifest decreased lymphocyte count (including marked depletion of NK cells) while secretion of inflammatory cytokines contributes to the cytokine storm. Dysregulated immune response in severe SARS-CoV-2 infection is marked by decreased lymphocyte counts, increased neutrophil counts, a higher neutrophil-lymphocyte ratio and an increased percentage of monocytes and macrophages that infiltrate the lung responsible for lung disease with eventual fibrosis.

**Cytokine Storm:** Neutrophilia and lymphocytopenia have been suggested as risk factors for the development of cytokine storm, ARDS, and progression from ARDS to death in severe COVID-19 (20). The mechanisms by which SARS-CoV-2 subverts the body's innate antiviral cytokine responses are under investigation as multiple viral structural and non-structural proteins can antagonize interferon responses. Antagonism or inadequate type I interferon response allows unchecked viral replication

triggering the intracellular processes that lead to increased pyroptosis with further aberrant inflammatory responses as part of massive cell destruction. The damaged cell products in-turn recruit proinflammatory macrophages and granulocytes and unrestrained inflammatory cell infiltration can itself mediate tissue damage through excessive secretion of proteases and reactive oxygen species, besides the direct damage resulting from the virus (21). Besides causing local damage in the lung, cytokine

storm also has ripple effects across the body. Elevated levels of cytokines can cause shock and multi-organ failure which can lead to myocardial injury and circulatory failure as observed in many patients with severe infection. People with severe COVID-19 seem to exhibit a phenomenon consistent with the "Macrophage Activation Syndrome" (MAS), a life-threatening condition that requires immediate medical attention (22). MAS is characterized by hyper stimulation and proliferation of macrophages and T cells causing an inflammatory cytokine storm by mediation of hemophagocytosis and hyper-cytokemia (22-24). Red blood cell (RBC) destruction in hemophagocytosis leads to release of high levels of ferritin. High ferritin levels are classically associated with inflammatory diseases and septic shock (23). Cytokine cocktail consisting of tumor necrosis factor and interferon-gamma and several interleukins (IL-1, IL-6, IL-10, IL-18, IL-33) are part of cytokine storm. Hence dampening of a hyper stimulated immune response using anti-inflammatory agents and steroids is an attractive therapeutic option besides novel treatments that modulate the release of cytokines. Anti-inflammatory therapies that attenuate NLRP3 inflammasome upstream or downstream, modulation of cytokines and/or agents that neutralize macrophages and neutrophils that work alone or in combination are also under evaluation as therapeutic agents.

In summary, pathology of severe COVID-19 infection involves multiorgan-hepatorenal, myocardial, lung damage attributable to multiple reasons like immune complexes, cytokine storm, vascular/endothelial dysfunction, coagulation disorders, and hypoxic injury (22). Old age and people with co-morbidities are more likely to develop such a dysfunctional immune response and may fail to eradicate the pathogen (25, 26). To demarcate the bane from the boon, we need to focus on aspects of the COVID-19 pandemic crucial to understand the disease severity and hence the considerations for clinical management of mild-moderate-severely ill patients and post COVID-19 sequelae. This review brings forth the scientific learnings to manage COVID-19 with the key thrust of decreasing pill burden and reducing morbidity and mortality based on current recommendations.

**The Changing Landscape and Current Status of Recommendations to Manage COVID-19:** The main strategy of clinical management of COVID-19 disease is focused on novel inhibitors, alleviating clinical symptoms and supportive care (27). The clinical therapeutic agents and mechanism in COVID-19 management are

summarized in Table 1 (28). Figure 2 summarizes clinical management of hospitalized and non-hospitalized COVID-19 patients (28). For hospitalized patients, the supportive treatment including oxygen therapy, conservation fluid management, and the use of broad-spectrum antibiotics to cover secondary bacterial infection, whereas anti-thrombotic and concomitant medication remains important in management strategy and decision should be made on case-by-case basis.

**Pre-exposure Prophylaxis (PrEP) for COVID-19:** The United States Food and Drug Administration (FDA) has granted Emergency Use Authorization (EUA) to Long-acting antibody (LAAB) treatment (29). LAAB is a pre-exposure prophylaxis (PrEP) beneficial for individuals not exposed to COVID-19 but are at high risk for severe COVID-19 and hospitalization, once infected (30). Combination of monoclonal antibodies Tixagevimab and Cilgavimabis is a LAAB treatment provided EUA by FDA (31). This cocktail can be administered to persons  $\geq 12$  years old, weight  $\geq 40$  kg with history of immune compromise or allergy to currently available vaccines against COVID-19 (31).

**Clinical Management and Treatment for Mild to Moderate Disease:** Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) do not initially require hospitalization, and maybe able to manage their illness at home. The decision to monitor a patient as inpatient or outpatient is made case-by-case. Home care for COVID-19 entails isolation in well ventilated room, adequate hydration, following respiratory etiquettes, hand hygiene, use of mask with frequent change for patient and caretakers, monitoring temperature, and oxygen saturation daily (32).

Patients at higher risk of severe illness should be monitored closely given the possible risk of progression to severe illness in the second week after symptom onset and may benefit from administration of monoclonal antibodies in outpatient or under hospital settings. Also, availability of new antivirals for patients with possibility of progression to severe disease/hospitalization/death and their current recommendation status (28) are elaborated below.

**Table 1: Clinical Therapeutic Agents, Mechanism in COVID-19 Management and Current Status**

No	Types of Therapeutic Strategies/Agents	Therapeutic Mechanism	Current Recommendation ( <a href="https://www.covid19treatmentguidelines.nih.gov/">https://www.covid19treatmentguidelines.nih.gov/</a> )
1	<b>Antivirals:</b> Nirmatrelvir 300 mg (two 150 mg tablets) and Ritonavir 100 mg	Nirmatrelvir is a protease inhibitor preventing viral replication. Ritonavir increases plasma concentrations of Nirmatrelvir	Emergency Use Authorization granted for early treatment of patients aged $\geq 12$ years and weighing $\geq 40$ kg within five days of onset of symptoms who possess high risk for progression to severe COVID-19, hospitalization or death
	Molnupiravir 800 mg (four, 200-mg capsules)	As synthetic cytidine nucleoside, Molnupiravir introduces errors during viral replication and thereby producing defective viral elements	Emergency Use Authorization granted for early treatment of patients aged $\geq 18$ years within five days of onset of symptoms who possess high risk for progression to severe COVID-19, hospitalization or death
	Remdesivir 200mg IV on Day 1 followed by 100mg IV from Day 2	Acts by shutting down viral replication by inhibiting a key viral enzyme, the RNA polymerase	Emergency Use Authorization for hospitalized adults and emergency use in individuals <i>aged <math>\geq 28</math> days and weighing <math>\geq 3</math> kg</i> Not recommended for mild -moderate COVID-19
	Ivermectin 200–600 $\mu$ g/kg	Blocks transmission of viral proteins into host nucleus by inhibiting the importin (IMP) $\alpha/\beta$ receptor	Not recommended for treatment of COVID-19, for PrEP or PEP for prevention of SARS-CoV-2 infection, except in a clinical trial
	Chloroquine or Hydroxychloroquine 800 mg loading dose followed by 400 mg	Chloroquine and hydroxychloroquine inhibit fusion of SARS-CoV-2 with host membrane/binding to receptor for cell entry/prevent release of viral genome thus exerting antiviral role. Also have immunomodulatory role.	Not recommended for treatment of mild-moderate-severe COVID-19.  Their Emergency Use Authorization was withdrawn in mid-2020
2	<b>Anti-inflammatory Agents:</b> Systemic Corticosteroids: Dexamethasone 6mg, Hydrocortisone 10mg, Prednisone 40mg, Methylprednisolone 32 mg	Directly target the key cytokines, dampens cytokine storm and alleviate hyperinflammation	To use Dexamethasone over other systemic corticosteroids for the treatment of hospitalized patients with severe or critical COVID-19 requiring supplemental oxygen. If Dexamethasone is not available, other systemic corticosteroids at dosages equivalent to Dexamethasone 6 mg daily may be used.  However, Dexamethasone is not recommended in mild to moderate COVID-19 and in clinically severe patients not requiring supplemental oxygen
	Inhaled Corticosteroids: Budesonide 800mcg Ciclesonide 160mcg		Currently, inhaled corticosteroids (Budesonide, Ciclesonide) are not recommended for treatment of COVID-19
	<b>Monoclonal antibodies (mAbs):</b> Casirivimab 600mg plus Imdevimab 600 mg IV  Bamlanivimab 700 mg plus Etesevimab 1400 mg IV  Sotrovimab 500 mg IV Bebtelovimab 175 mg IV  Tixagevimab 300 mg plus Cilgavimab 300 mg IM	Neutralizing antibodies that block viral attachment and binding to the SARS-CoV-2 receptor-binding domain of the Spike protein thus blocking virus entry	Initially, Emergency Use Authorization granted for Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab and Sotrovimab for post exposure prophylaxis (PEP) and treatment of mild to moderate cases of COVID-19. However, in January 2022, use of these monoclonal antibodies was withdrawn as found ineffective against different Omicron COVID-19 variant.  Bebtelovimab effective against Omicron variants is still recommended for treatment of high-risk outpatients with mild to moderate COVID-19  Tixagevimab plus Cilgavimab is recommended as preexposure prophylaxis (PrEP) of COVID-19 for patients at high risk of infection

4	<p><b>IL-6 Inhibitors:</b></p> <p>Anti-IL-6 receptor mAbs: Tocilizumab: &lt;30 kg: 12 mg/kg IV (maximum 800 mg) ≥30 kg: 8 mg/kg IV (maximum 800 mg)</p> <p>Sarilumab 400 mg SQ in 100 cc 0.9% NaCl administered IV anti-IL-6 mAbs: Siltuximab</p>	<p>Anti-Interleukin-6 Receptor Monoclonal antibodies</p>	<p>Tocilizumab use recommended with Dexamethasone for hospitalized patients with COVID-19 who are receiving invasive mechanical ventilation or ECMO and who are within 24 hours of ICU admission with rapid respiratory decompensation</p> <p>Recommended only when Tocilizumab is not available or is not feasible to use</p> <p>Not recommended for COVID-19 patients except under clinical trials</p>
5	<p><b>Interleukin-1 Inhibitors</b></p> <p>Anakinra 300 mg/200 mg/100 mg IV</p> <p>Canakinumab 450 mg/ 600 mg/ 750mg</p>	<p>IL-1 inhibitors</p>	<p>Anakinra and Canakinumab are not recommended in the treatment of COVID-19, except in clinical trials</p>
6	<p><b>Kinase inhibitors:</b></p> <p>Baricitinib 4 mg/2 mg/1mg</p> <p>Tofacitinib 10 mg</p> <p>Ruxolitinib 5 mg-20 mg</p>	<p>Involved in signaling pathways that can regulate cytokines responsible for cytokine storm</p>	<p>Baricitinib and Tofacitinib are recommended in certain hospitalized patients while Ruxolitinib is not recommended.</p> <p>In rare circumstances when corticosteroids cannot be used, the use of Baricitinib/ Tofacitinib in combination with Remdesivir and Dexamethasone for the treatment of COVID-19 in hospitalized non intubated patients who require oxygen supplementation is recommended</p>
7	<p><b>Angiotensin Receptor Blockers (ARB)</b></p>	<p>Potentially beneficial vasodilatory and anti-inflammatory properties, blocking enzymatic activity that aids in viral clearance</p>	<p>Patients receiving an ACE inhibitor or ARB for cardiovascular disease (or other non-COVID-19 indications) should not discontinue these drugs during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition.</p> <p>However, ACE inhibitors or ARBs should not be used to treat COVID-19 except in the context of a clinical trial</p>
8	<p><b>Antithrombotic Agents</b></p>	<p>Reduces the formation of blood clots by inhibiting platelet activity</p>	<p>It is recommended to use a venous thromboembolism (VTE) prophylactic dose of low molecular weight heparin for patients in ICU or requiring high flow oxygen.</p> <p>Patients hospitalized with COVID-19 already receiving anticoagulant or antiplatelet therapy should not discontinue use unless contraindications are present or significant bleeding develops.</p> <p>Patients with no signs or symptoms of VTE should not be given any antithrombotic therapy.</p> <p>VTE prophylaxis for patients with COVID-19 after hospital discharge is not recommended.</p>
9	<p><b>Convalescent Plasma</b></p>	<p>Modifying the inflammatory response, provides immediate immunity</p>	<p>The use declined in early 2021 due to mixed results from randomized clinical trials.</p> <p>Recommended for use based on individualized assessment of risk and benefit/ immunosuppressed patients with aberrant antibody responses</p>
10	<p><b>Adjunct Therapies</b></p>	<p>Immunomodulatory role</p>	<p>Vitamin and mineral supplements like Vitamin C, D and Zinc are not recommended as adjunct therapies for treatment of COVID-19</p>

Scenario	Key recommendations
Pre-exposure prophylaxis (PrEP) for high risk individuals	<p>Long acting antibody treatment</p> <ul style="list-style-type: none"> <li>Tixagevimab and Cilgavimab (Evushed) (Monoclonal antibodies)</li> </ul>
Mild to Moderate COVID-19	<p>Symptomatic management only</p> <p>For patients who are at high risk of progressing to severe COVID-19</p> <ul style="list-style-type: none"> <li>Ritonvir-boosted Nirmatrelvir (Paxlovid) (anti-viral)</li> <li>Molnupiravir (anti-viral)</li> <li>Bebtelovimab (Monoclonal antibodies)</li> </ul>
Hospitalized but supplemental oxygen not required	<p>Dexamethasone and other corticosteroids NOT RECOMMENDED</p> <p>Remdesivir RECOMMENDED in case of high risk of disease progression</p> <p>Prophylactic dose of heparin without evidence of VTE</p>
Hospitalized with incremental oxygen requirement	<p>Use either one option:</p> <ul style="list-style-type: none"> <li>Remdesivir (anti-viral)</li> <li>Dexamethasone (steroid) plus remdesivir (anti-viral)</li> <li>Dexamethasone (steroid)</li> <li>Therapeutic dose of heparin with D-dimer levels &gt; Upper Limit of Normal else Prophylactic dose of heparin without evidence of VTE</li> </ul> <p>For rapidly increasing oxygen demand add Baricitinib/Tocilizumab (JAK Kinase inhibitor) to either option above</p>
Hospitalized and requires oxygen through a high-flow device or Non-invasive ventilation	<p>Use either one option:</p> <ul style="list-style-type: none"> <li>Remdesivir (anti-viral)</li> <li>Dexamethasone (steroid) plus remdesivir (anti-viral)</li> <li>Prophylactic dose of heparin without evidence of VTE</li> </ul> <p>For rapidly increasing oxygen demand and systemic inflammation add Baricitinib/Tocilizumab (JAK Kinase inhibitor) to either option above</p>
Hospitalized and requires Mechanical Ventilation or ECMO	<p>Dexamethasone (steroid)</p> <p>For patients who are within 24 hours of admission to the ICU:</p> <ul style="list-style-type: none"> <li>Dexamethasone (steroid) plus IV Tocilizumab / Sarilumab (IL6 Inhibitor)</li> <li>Prophylactic dose of heparin without evidence of VTE</li> </ul>

**Figure 2: Recommendations to Manage Different COVID-19 Scenarios:** Long acting antibody treatment is recommended for high risk individuals on pre-exposure prophylaxis. Symptomatic management to be considered for mild to moderate cases of COVID-19 but if the condition can transform to severe COVID-19 then treatment with Ritonvir- boosted Nirmatrelvir, Molnupiravir, and Bebtelovimab is recommended whereas when a patient is hospitalized due to COVID -19 but doesn't require supplemental oxygen then Dexamethasone and other corticosteroids are not recommended but Remdesivir is recommended in case of high risk of disease progression. Patients hospitalized due to COVID -19 and require incremental oxygen can be treated with various options such as Remdesivir, Dexamethasone, combination of both Remdesivir and Dexamethasone, and therapeutic dose of heparin when D-dimer levels are greater than upper limit of normal, else prophylactic dose of heparin without evidence of VTE is recommended. However, in case patient needs oxygen with high flow device or non-invasive ventilation then treatment will be the same as done for the patient requiring incremental oxygen excluding therapeutic dose of heparin. Dexamethasone is recommended for patient hospitalized and requiring mechanical ventilation or ECMO but when patient have been admitted to ICU within 24 hours then Dexamethasone with IV Tocilizumab / Sarilumab (IL6 Inhibitor) and Prophylactic dose of heparin without evidence of VTE is recommended.

**a) Antibody Preparations:** Immunotherapy is regarded as an effective method for clinical treatment of infectious diseases. Human monoclonal antibodies are promising therapeutic molecules successfully used for the prevention or treatment of viral infectious diseases (33). Recent years have seen major advances in human B cell isolation techniques and have led to the identification of large numbers of therapeutic monoclonal antibodies candidates against many life-threatening viral pathogens.

Using monoclonal antibodies in infectious disease prevention may overcome many drawbacks associated with serum therapy and intravenous immunoglobulins preparations in terms of specificity, purity, low risk of blood-borne pathogen contamination and safety. In recent years, many monoclonal antibodies against viruses are being developed and some are already in clinical pipeline (34- 36). Harnessing and identifying cells producing neutralizing antibodies from sera of recovered individuals and generating blocking monoclonal antibodies is an attractive strategy (37).

The spike protein present on the surface of the coronavirus is one of the principal antigenic components against which immune responses are generated. The specific neutralizing monoclonal antibodies either against receptor-binding domain in spike protein or specific antibody that binds to ACE2 could effectively block the virus entry. Hence, these were a key target to develop potential effective therapeutics against Coronavirus infection (37).

Two monoclonal antibody cocktail- Casirivimab and Imdevimab - bind to different epitopes of the RBD of spike protein non-competitively and have shown potent virus neutralization by blocking the interaction of the viral protein with ACE2 (38). This would be helpful as both prophylaxis and as a treatment measure especially in high-risk groups. The antibody cocktail was approved by USA FDA under EUA in adults with mild-to-moderate COVID-19 to prevent progression to severe disease in high-risk individuals with poor prognosis.



The BLAZE trial-Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies showed relevance of anti-spike neutralizing monoclonal antibodies- Bebtelovimab alone or with Bamlanivimab and Etesevimab in reducing viral loads in mild-moderate patients leading to their EUA (39). Sotrovimab, another neutralizing monoclonal antibody inhibiting SARS-CoV-2 replication and prevented disease progression to severe COVID-19 was granted EUA after successful results of TICO-ACTIV-3 trial (40).

In January 2022, the EUA of Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, and Sotrovimab for post exposure prophylaxis (PEP) and treatment of mild to moderate cases of COVID-19 was withdrawn due to their ineffectiveness against Omicron COVID-19 variants. Bebtelovimab effective against Omicron variants is still recommended for treatment of high-risk outpatients with mild to moderate COVID-19 (28). The recommendations for monoclonal antibodies therapy remains fluid and requires cognizance of prevailing COVID-19 variants and subvariants.

**b) Antiviral Agents:** With onset of symptom less than 5 days, The FDA recommends Nirmatrelvir and Ritonavir or Molnupiravir for patients with possibility of progression to severe disease/hospitalization/death (26). Dual pill Nirmatrelvir and Ritonavir is the recent most addition to the EUA list of COVID-19 drugs. In a phase 2/3 EPIC-HR clinical trial involving 2224 non-hospitalized adult patients with confirmed diagnosis of COVID-19 with risk of progression to severe disease, Nirmatrelvir and Ritonavir reduced hospitalization time and death by 86% compared to placebo group (41). The drug was most effective in clearing the virus within three days of symptom onset. The combination drugs are authorized for use amongst the age group above 12 years weighing 40 kg, while it is not advised in patients with renal and hepatic impairment.

Molnupiravir, an oral, small-molecule antiviral pro-drug was evaluated in 1433 participants in a Phase 3 MOVE-OUT randomized, placebo-controlled, double-blind clinical trial (42). The participants included non-hospitalized, mild-to-moderate confirmed COVID-19 cases at risk for progressing to severe COVID-19. Early treatment, before 5 days of symptoms onset, with Molnupiravir reduced the risk of hospitalization or death by COVID-19 in at-risk, unvaccinated adults (42).

***Clinical Management and Treatment for Severe Disease:***

Severe illness management revolves around the supportive management of the complications of severe COVID-19 that include sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury and complications from prolonged hospitalization including secondary bacterial/fungal infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Acute hypoxemic respiratory failure from ARDS is the most common complication in patients admitted to the ICU, followed by shock, myocardial dysfunction, and acute kidney injury. In a small proportion of these, the illness may be severe enough leading towards death. Besides therapeutic interventions, proning for 12 hours a day with side switching every two hours has reduced mortality in ARDS patients with severe hypoxia. Use of therapeutic agents to manage disease progression or to manage advent of severe disease are elaborated below along with their current status of recommendations (28).

**a) Antiviral Agents:** The dilemma is whether to “Target Virus or Target Ourselves” for COVID-19 (43). Several clinical trials are being conducted to determine which therapeutic targeting could potentially present more effective and broad-spectrum treatment modalities for COVID-19. One strategy adopted is to repurpose approved drugs known to act on different stages of both the infection and host response. Most of these drugs were originally designed for other pathogens and now repurposed for treatment of COVID-19 as these drugs are reported to have favorable safety profiles. These therapies can be divided into two categories depending on their target. One therapeutic approach primarily target virus directly either by blocking viral entry to human cells or by inhibiting viral enzymes responsible for replication. The other approach includes drugs that interfere with signaling pathways involved in viral replication or host innate immune responses.

Most antiviral drugs are small-molecule inhibitors and exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoded enzyme, blocking virus particle formation, or targeting a host factor required for replication (44). Repurposed existing drugs include an experimental antiviral Remdesivir; the malaria medication Chloroquine (or its chemical cousin Hydroxychloroquine); a combination of the HIV drugs Lopinavir and Ritonavir; and combination of Lopinavir and Ritonavir plus interferon-beta, which acts

as an immune system messenger, that can help cripple viruses. These treatments may stop the virus replication by different mechanisms, but each has drawbacks.

**Remdesivir:** Remdesivir is a monophosphoramidate pro-drug of an adenosine analogue with a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. *In vitro*, Remdesivir has shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV including SARS-CoV-2 infections (45). Remdesivir has been found to inhibit coronavirus replication and improve pulmonary functions prophylactically and therapeutically (in early stage of infection) based on evidence from both *in vitro* and *in vivo* experiments. Remdesivir was developed by Gilead Sciences (USA) originally against the Ebola virus. While not effective against Ebola, the drug proved its safety in humans, and this allowed repurposing of the drug in clinical trials immediately in COVID-19 on an emergency basis (46). Remdesivir acts by shutting down viral replication by inhibiting a key viral enzyme, the RNA polymerase. The drug, which is given intravenously, has been issued FDA and EU Emergency Use Authorization to treat hospitalized patients aged  $\geq 28$  days and weighing  $\geq 3$  kg (26). Clinical studies showed that patients treated with Remdesivir had higher recovery rates and were associated with better rates of hospital discharge, but there was no significant reduction in mean time to clinical improvement or mortality (47). When mortality risk is low, using Remdesivir is not recommended (28).

**Lopinavir-Ritonavir Combination with or without Interferon:** Lopinavir is an antiretroviral drug and acts as a protease inhibitor and is usually formulated with another protease inhibitor Ritonavir which decreases the metabolism of Lopinavir by the inhibition of cytochrome P450. Lopinavir-Ritonavir is approved to treat HIV/AIDS (48). Although preliminary clinical trials using Lopinavir-Ritonavir to treat SARS-CoV-2 have been disappointing (49), it is being evaluated combined with other antiviral drugs (50). No significant benefit was observed with Lopinavir-Ritonavir treatment beyond standard care. Diarrhoea, nausea, and asthenia were the most frequently reported adverse effects in patients receiving Lopinavir-Ritonavir based regimen (51). Results from various clinical studies have shown there was no benefit of using Lopinavir-Ritonavir in reducing mortality rate, hospital time nor progression to mechanical ventilator intervention in COVID-19 patients. Hence not recommended for treatment of COVID-19.

**Favipiravir:** Favipiravir is a non-nucleoside RNA polymerase inhibitor and acts by dysregulating viral RNA replication. Favipiravir showed antiviral activity against infectious diseases caused by RNA viruses such as Influenza, Ebola, and Norovirus Influenza A, yellow fever, and Ebola (52-53). Favipiravir was repurposed as an experimental agent for COVID-19. A randomized control trial showed that COVID-19 patients treated with Favipiravir had better recovery rate (71.43%) than those treated with Umifenovir (55.86%), and the relief from fever and cough was significantly faster in Favipiravir group than in Umifenovir group (54). In a study from India, early virological clearance was observed in adults with mild to moderate COVID-19 that received Favipiravir, although not statistically significant and requires more evaluation for long-term use (55), hence not recommended for treatment of COVID-19.

**Oseltamivir:** Oseltamivir is a well-tolerated neuraminidase inhibitor drug approved for treatment of Influenza A and B that reduces viral shedding and severity of illness (56). An early study from Wuhan reported no improvement in COVID-19 patients administered different doses of Oseltamivir (57) and thus not used in COVID-19 treatment.

**Chloroquine:** Chloroquine (CQ) and the 4-aminoquinoline drug hydroxychloroquine (HCQ), amine acidotropic form of natural quinine is an approved front-line drug for the treatment and prophylaxis of malaria (58). CQ and HCQ were initially touted as potential broad-spectrum antiviral drugs and can block virus infection by increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cellular receptors of SARS-CoV (59). CQ has been shown to interfere with the terminal glycosylation of ACE2, and thus negatively influences the virus-receptor binding in SARS-CoV infection (59-61). CQ and HCQ can also inhibit major histocompatibility complex class II expression, antigen presentation and immune activation (reducing CD154 expression by T cells) via Toll-like receptor signaling and cGAS stimulation of interferon genes. Thus, CQ and HCQ can reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon- $\alpha$  and tumor necrosis factor, which are involved in the cytokine storm. The immunomodulatory effects of CQ may synergize its antiviral effects in the treatment of COVID-19 (62). Whether HCQ is as efficacious as CQ in treating SARS-CoV-2 infection still lacks experimental evidence. Medical opinion has cautioned that HCQ can prove more harmful than doing any good as it poses numerous side effects. As in controlled clinical trials CQ and HCQ have failed to demonstrate benefit for treating

COVID-19, these are not recommended for treatment of COVID-19 (28).

**Ivermectin:** Macrocyclic lactone Ivermectin is reported to have antiparasitic, antiviral and immunomodulation roles in human host. Regarding COVID-19, Ivermectin blocks transmission of viral proteins into host nucleus by inhibiting the importin (IMP)  $\alpha/\beta$  receptor (63). Ivermectin was considered a potential anti-viral when tested as a prophylactically (NCT04422561) in early stages of COVID-19 infection as a host directed therapy to reduce viral load to levels where the host immunity can control the infection. Some observational and case control studies and small randomized clinical trials suggest a potential benefit of Ivermectin. The pilot study report that in group treated with ivermectin there was marked reduction of self-reported anosmia/hyposmia, a reduction of cough, lower viral loads and lower IgG titers (64). Although seems promising, larger trials needed to support use of Ivermectin for the early treatment of COVID-19. To date controlled clinical trials have failed to substantiate the clinical benefit in COVID-19 illness and hence not recommended for treatment of COVID-19 (28).

**Azithromycin:** A macrolide with an established safety profile, Azithromycin has exhibited *in-vitro* antiviral activity by acting at different stages of the viral cycle and immunomodulatory activities of dampening the cytokine storm. The drug can achieve therapeutic concentrations in the lung is useful in community acquired pneumonia. The RECOVERY trial, however reported that Azithromycin 500 mg for 10 days may benefit individuals with bacterial infections only and did not reduce 28-day mortality in patients hospitalized with COVID-19 (65), an eye opener to prevent resistance development by rampant misuse of such macrolide antibiotics.

**b) Anti-inflammatories and Immunomodulators:** In SARS-CoV-2 infection, infiltration of large number of inflammatory cell and cytokine storm lead to acute lung injury, ARDS and death (66-70). Most of severe COVID-19 patients have persistent high levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and high level of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, TNF $\alpha$  associated with ARDS, hypercoagulation and disseminated intravascular coagulation (DIC), manifested as thrombosis, thrombocytopenia, gangrene of extremities. Maybe cytokine storm exacerbates lung damage and leads to other fatal complications. In severe illness, abrupt deterioration is noticed within 1–2 weeks after disease onset. As cytokine storm occurs in critically ill

patients leading to the immune-mediated damage and even death in some cases, giving priority to targeting the inflammatory response could blunt the inflammatory cytokine storm and help in checking further tissue injury.

Several approaches including immunomodulatory agents that directly target the key cytokines involved in COVID-19 may help to alleviate hyperinflammation symptoms in severe cases and cope with cytokine storm. Monoclonal antibodies blocking cytokines associated with hyperinflammation is a promising therapeutic avenue to limit systemic inflammation before it results in multi-organ dysfunction in COVID-19 patients. Certain immunomodulatory agents with good safety profiles may be considered for combination with antiviral drugs to treat severe or critical cases of COVID-19 as elaborated below.

**IL-6 Inhibitors:** Among the increased level of cytokines produced, elevated levels of the inflammatory indicator IL-6 in the blood have been reported to be predictive biomarker for disease severity. IL-6 binds to transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and the resulting complex can combine with signal transducing component gp130 to activate the inflammatory response. Tocilizumab is a specific monoclonal antibody IL-6 receptor antagonist that can bind specifically to sIL-6R and mIL-6R, and block signal transduction (71). Thus, monoclonal antibodies against IL-6 could theoretically dampen cytokine storm process and improve clinical outcomes. Dose of 8 mg per kilogram of body weight intravenous Tocilizumab was evaluated in phase 3 EMPACTA (Evaluating Minority Patients with Actemra) clinical trial in hospitalized COVID-19 patients without mechanical ventilation (72). The results showed that Tocilizumab added to benefits of antivirals and glucocorticoids in saving lives as also substantiated by many trials globally including the RECOVERY trial. Tocilizumab is recommended in critical patients with high oxygen demand and acute inflammatory response (28). Likewise, Sarilumab another anti-IL-6 receptor mAbs is approved for use in hospitalized patients when Tocilizumab is not available while Siltuximab- anti-IL-6 mAbs is not recommended in COVID-19 treatment except in clinical trial (28).

**IL-1 Inhibitors:** There is a battery of other biological agents available that target various other critical cytokines in the inflammatory network and repurpose their anti-inflammatory activities to treat COVID-19. The recombinant IL-1 receptor antagonist, Anakinra was originally developed

to control cytokine storm and associated tissue damage in sepsis patients and has subsequently been successfully used in patients with cytokine storm syndrome secondary to autoimmune/ inflammatory infectious or malignant disease (73). Anakinra was thought to have potential for controlling hyper-inflammation in severe COVID-19 disease (74) but is not currently recommended along with another IL-1 mAbs-Canakinumab (28).

**Corticosteroids:** Dexamethasone used in severe asthma, allergies, painful and swollen joints, systemic lupus erythematosus and rheumatoid arthritis was repurposed as an easily available and affordable drug to treat severe cases of COVID-19. Dexamethasone lessens the cytokine storm and dampens the immune response thus preventing the huge inflammation evident in lung and heart leading to acute respiratory issues in severely ill patients. Dexamethasone has been tested in the largest COVID-19 drug trial called the Randomized Evaluation of COVID-19 Therapy or RECOVERY trial (75). As part of the trial, researchers studied the effect of 6 mg daily dose of dexamethasone for 10 days in patients and compared that to the patients who did not receive it. The results of the trial showed the greatest benefit was in those patients on ventilators, where dexamethasone reduced the risk of death. In the cohort, 29.3% vs. 41.4% deaths respectively were reported in dexamethasone group compared to subjects on mechanical ventilation: 23.3% vs. 26.2% respectively in the group receiving dexamethasone and oxygen without mechanical ventilation and 17.8% vs 14.0% respectively in the group with dexamethasone and with no respiratory support (75). This translates to one life saved for every eight on ventilators and one in every 20-25 treated with oxygen. The drug is not proven to be beneficial in those with mild symptoms who do not require respiratory support. Brazil CoDEX trial also showed that Dexamethasone is the drug of choice to reduce mortality from COVID-19 (76). Use of alternative corticosteroids like hydrocortisone, prednisone, methylprednisolone for patients with severe COVID-19 are also recommended while inhaled corticosteroids Budesonide and Ciclesonide are not recommended (28). A word of caution that use of corticosteroids in the treatment of COVID-19 can cause immune suppression and may delay the elimination of virus and increase the risk of secondary infections.

**Janus Kinase (JAK) Inhibitors:** Given the nature of the COVID-19 cytokine storm and considering substantial impairment of host immune system in severe cases, it is critical to balance the risk and benefit before starting anti-

inflammation therapy. In addition, timely anti-inflammation treatment initiated at the right window time is pivotal and should be tailored to individual patients to achieve the most favorable effects. However, there are many concerns with anti-inflammatory medications. The critical issue is balancing the risk and benefit ratio of anti-inflammatory therapy in COVID-19 infection. Anti-inflammation therapy that specifically target one set of pro-inflammatory cytokines may inhibit that specific inflammatory factor but fail in curbing the cytokine storm in COVID-19 in which other cytokines maybe of significant importance. Third, some anti-inflammation medication such as Janus kinase (JAK) inhibitor like Tofacitinib block INF- $\alpha$  production, which is important in controlling virus replication, and theoretically may not be suitable to treat inflammatory cytokine storm caused by COVID-19. On the contrary, other JAK inhibitors like Baricitinib was useful in managing cytokine storm by blocking cytokine signaling pathways and reducing hospital stay when co-administered with Remdesivir (77). Baricitinib/ Tofacitinib and Tocilizumab is recommended with Dexamethasone alone or Dexamethasone with Remdesivir to treat COVID-19 in critically ill hospitalized patients requiring high flow oxygen with systemic inflammation (28).

**c) Antithrombotic Therapy:** COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and venous thromboembolism (VTE). Both thrombotic risk assessment and VTE prevention are important components of the complex and comprehensive treatment of COVID-19 infection. Given that some COVID-19 patients' conditions may rapidly change, resulting in dynamic modifications of thrombotic risk and bleeding during treatment, repeated assessment and optimized strategies are crucial to reduce VTE and prevent fatal pulmonary embolism (PE) and effectually safeguard patients and promote early recovery. Experts have expressed consensus on management of COVID-19 associated VTE and preferential thromboprophylaxis measures based on VTE risk scoring, kidney function, creatinine clearance and severity of diseases along with anticoagulants (78-80). Low molecular weight heparin is recommended as the first line of treatment in severe and critically ill COVID-19 patients with low risk of bleeding (28). The experts have also recommended against non-heparin drug use like rivaroxaban or fondaparinux in presence of co-morbidities in critically ill COVID-19 patients. As coagulation parameters like D-dimer provide prognostic values, they are valuable to determine the risk

of developing VTE and may prompt consideration of full therapeutic dose regimens. It is not advised to continue VTE prophylaxis for discharged COVID-19 patients (28). The decision to continue post-discharge VTE prophylaxis should be based on case-by-case risk assessment for VTE, and bleeding.

**d) HMG Co A Reductase Inhibitors (Statins), ACE Inhibitors, and Angiotensin Receptor Blockers (ARBs):** Patients who suffer from hypertension and heart disease are treated with renin-angiotensin system (RAS) blockers, angiotensin receptor blockers (ARBs) and HMG-CoA reductase inhibitors/statins. RAS inhibitors and statins act by up-regulating ACE2 receptors and theoretically this could enhance viral entry leading to worsening outcomes. They were proposed to have a potential role in managing patients with severe COVID-19 due to immunomodulatory and anti-inflammatory role to reduce tissue injury through production of angiotensin [1-7] (81-82). The controversy regarding statins in treating severe COVID-19 along with ACE inhibitors and ARBs has finally been put to rest. Patients receiving these as concomitant medications for an underlying medical condition should not discontinue such therapy (28, 83). It is suggested that statins/ACEIs/ARBs should not be initiated in those patients with COVID-19 without clinical indications of cardiovascular diseases (28).

Acute treatment with statins had no significant effect on the course of SARS-CoV-2 infection. However, if a COVID-19 patient is earlier exposed or treated with statins then it can decrease the death risk in a patient who is hospitalized but not admitted in ICU (84). There is consensus on the fact that when cholesterol is lowered with statins, it has an advantageous impact on COVID-19 as presence of high amount of cholesterol in cell membranes eases the entry of SARS-CoV-2 through pushing ACE2 into endocytic vesicles, potentially becoming one phenomenon of age-related risk for COVID-19 (85). Thus, long term therapy with statins are being evaluated for COVID-19 outcomes in high-risk groups.

#### ***Agents Under Lens for Management of COVID-19***

**Convalescent Plasma:** Convalescent Plasma (CP) therapy is a classic adaptive immunotherapy and has been applied to the prevention and treatment of many infectious diseases. Convalescent serum was used during H1N1 pandemic, SARS, MERS and Ebola outbreaks with effective efficacy and safety (86-89). A general principle of CP therapy states it proves to be effectual to a greater extent when not used in treatment but for prophylaxis. If using in the therapy,

antibodies are touted to be effective when regulated in a shorter span of time right after the first day of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease (90-91). A different explanation could be that modification of inflammatory response could be possibly the reason to how antibody works, since inflammatory can easily be obtained in the commencing of the immune response (91). Convalescent plasma therapy was hence considered as an option to treat the disease since it had demonstrated possible benefit in other coronaviruses outbreaks (92-94). Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of CP.

The administration of CP was initially recommended to treat or prevent ARDS induced by SARS-CoV-2 infection and to accelerate virus clearance. The infusion of hyperimmune convalescent plasma having anti-IgG specific SARS-CoV-2 antibodies obtained from PCR-negative, COVID-19 recovered patients were an attractive approach in newly infected subjects. Duan et al reported that one dose of 200 mL CP transfusion was well tolerated by the critically ill patients with laboratory confirmed COVID-19 (95). After receiving plasma transfusion, the clinical symptoms significantly improved with the increase of oxyhemoglobin saturation within 3 days, increased lymphocytes count, and reduced level of C-reactive protein accompanied by rapid neutralization of viremia and with no adverse effects. However, there are various downsides to this approach which includes the difficulty in scaling up for widespread use as well as the risk of transmission of other diseases that would come along with the plasma of recovered patients. Also, the antibodies present in the plasma generally are in lesser concentration that may not be enough for the treatment. Use of CP therapy is investigational; clinical trials are assessing the true effectiveness of this therapeutic strategy (96-98). The current recommendations are against CP collected before the emergence of Omicron variants to treat COVID-19 (28, 98). Also, using CP in immunocompetent hospitalized patients is not recommended, yet immunocompromised COVID-19 patients with aberrant immune response may benefit from CP (28, 99). In such a case, individualized response to CP must be monitored carefully.

***Experimental Therapeutics for COVID-19:*** Purinergic signaling pathway modulated through extracellular purine

nucleotides and adenosine/ATP nucleosides hold promise as therapeutic strategy to address cytokine storm, especially through adenosine A2a, A2b and P2X7 receptors (100, 101). Extracellular ATP being part of DAMPs may have key role in cell signaling and is also suggested to be part of NLRP3 inflammasome activation that stimulates caspases and proinflammatory cytokines in response to cellular damage (102). Deregulation of the activity of CD39, a vascular ectonucleotidase, is involved in the thromboinflammation in COVID-19 (103). Change in CD39/CD73 axis, which helps in maintaining the balance between the activities of P1 and P2 purinergic receptors through sequential hydrolysis of extracellular ATP to adenosine, plays a role in the regulation of T cells in COVID-19 (104). These recent findings present very promising therapeutic strategies to tame or suppress cytokine storm in COVID-19.

The battle with COVID-19 lead to unprecedented attempts at repurposing plethora of drugs for existing diseases. Though repurposed drugs are reported to be predominantly safe, the human endeavors to win COVID-19 resulted in exceptional activity of repurposing drugs. The infamous drug thalidomide known for its teratogenicity showed promise in suppressing cytokine storm in severe COVID-19 (105). Thalidomide potentially inhibited chemotaxis of neutrophils and suppressed neutrophils and monocytes. It acts on several factors to downregulate the cytokine storm and independently suppressed the associated oxidative stress. Thalidomide being an up-regulator for NK and T cells can also reverse the downregulatory effect of COVID-19 (105).

Suramin, another highly neurotoxic drug used to treat parasitic infections, viral diseases and cancers has demonstrated remarkable ability to suppress SARS-CoV-2 entry and replication in cell cultures and thus merits evaluation in clinical trials (106).

The human saga to save lives of COVID-19 patients have brought forth many unconventional therapeutic approaches, yet their utility and adoption must be justified by strong scientific evidence and ethics.

**Summary and Conclusions:** As COVID-19 pandemic intensified, showed blips and ripples due to emergence of new variants, the disease is not yet eliminated. Global vaccination efforts along with the search for effective treatments and vaccines to control the disease are at the forefront of medical research. Globally, all possibilities are being explored including repurposing existing drugs used to treat HIV/AIDS, malaria, cancer, immune disorders and

evaluating them in well-planned clinical studies. Besides, new drugs in the form of small molecules targeting SARS-CoV-2 receptors, protease inhibitors, monoclonal antibodies, immunomodulators, antivirals, stem cell therapies and gene silencing approaches that prevent SARS-CoV-2 replication are being explored along with vaccine development. The ever-evolving pipelines with their current status are available at clinical trial database ([https://clinicaltrials.gov/ct2/who\\_table](https://clinicaltrials.gov/ct2/who_table)).

As the hunt for best remedies continue, the clinical management practice should include evaluation of all COVID-19 patients for the risk of developing cytokine storm and VTE. Antivirals would provide greatest benefit in the early course of the disease when viral replication can be slowed down. Once cytokine storm develops, antiviral treatment alone will not be enough and immune-suppressive/anti-inflammatory treatment will be necessary to dampen the cytokine storm. Early recognition and treatment of cytokine storm will decrease the morbidity and mortality in COVID-19 infection. We propose "800 rule"-Ferritin over 800 ng/ml and absolute lymphocyte count below 800 cells per cubic millimeter of blood. Combination of the "800 rule" and evidence for fever and organ dysfunction portends a high risk regardless of age. COVID-19 can cause pneumonia due to infiltration of macrophages and neutrophils; can lead to vasculitis with veno-occlusive pulmonary disease; *in-situ* pulmonary arterial thrombosis leading to profound refractory hypoxemia and in some individuals permanent end organ lung damage due to fibrosis and fibro-cavitary disease; systemic arterial and venous thromboembolism, cryptogenic strokes, and acute kidney injury. A graded approach to management of COVID-19 patients would thus include (a) low risk individuals will benefit from isolation, symptomatic management, prevention of transmission strategies and monoclonal antibodies therapy in non-hospitalized patients if at risk for severe disease, (b) all hospitalized patients (including mild and moderate with hypoxia) would benefit from an effective anti-viral (most likely combination therapy) as this is an RNA virus with a high replication rate that is a risk factor for serious disease, (c) at risk for cytokine storm (800 rule and fever) require use of Dexamethasone/anti-inflammatory to dampen the immune response besides standard treatment and antivirals. Furthermore, the sequelae of COVID-19 regarding vasculitis, cardiac, neurological, psychiatric manifestations, secondary bacterial and fungal infections need to be managed case-by-case as per existing standards of care and treatment.

The guidelines for management of severe COVID-19 are continuously evolving as new data from clinical trials emerge. As of now, hospitalized patients with severe COVID-19 with oxygen requirement without delivery through a high flow device or noninvasive ventilation would benefit from Remdesivir or Dexamethasone plus Remdesivir if the requirement for oxygen increases or Dexamethasone alone Remdesivir is not available. While alternative corticosteroid can be used if Dexamethasone is not available or Baricitinib plus Remdesivir can be used in absence of corticosteroids. Tocilizumab could be added to Dexamethasone treatment with C-reactive protein (CRP) levels  $\geq 75$  mg/L and increasing oxygen needs without need of noninvasive ventilation. However, benefits of addition of Tocilizumab need to be ascertained as it may lead to increased risk of opportunistic infections. Proning position facing ventilator, upto 12 hours in a day with switching sides every two hours, has benefited ARDS patients on sedatives. However, proning with low tidal volume (6 cc per kg body weight) with muscle and nerve relaxants is justified when the patient is hemodynamically stable. For hospitalized patients requiring Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation (ECMO), monotherapy with Dexamethasone or alternative corticosteroids is the best option. For patients who advanced to invasive ventilation or ECMO, it is recommended to start Dexamethasone and continue Remdesivir till the end of treatment.

Concomitant medications for underlying conditions that necessitate use of ARBs, ACE inhibitors, statins, systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs should not be discontinued. Using off-label treatment for COVID-19 should not be encouraged unless safety and efficacy of the therapy has been proven in clinical trials. Plethora of agents such as macro and micronutrient supplementation have also not contributed to obtaining any result in treatment for COVID-19. It has been noted that the pill burden should not be increased by indiscriminate use of macro and micronutrients i.e., zinc, vitamin C, vitamin D etc. as they have yielded no gains in combating COVID -19.

The emphasis should be on CAB (COVID-19 behavior) and JAB (COVID-19 Vaccination) as prevention strategies, till an ultimate solution for the pandemic is attained. Finally, one is reminded of Dr. David Ho's most elegant comment "*It is the Virus Stupid*"; we need to step up and tame it.

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## Clinical Study

# Preventing Hospitalization with Early Corticosteroid Treatment in COVID-19 Patients: A Retrospective Study

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**Background:** Pathophysiology of severe Coronavirus disease 2019 (COVID-19) includes microvascular endothelial inflammation, widespread microvascular thrombosis from activation of multiple inflammatory pathways. Anti-viral drugs do not curtail systemic inflammatory response. Anti-inflammatory agents, such as corticosteroids could affect the disease course and thereby reducing the morbidity and mortality of COVID-19 infection. This was evident from RECOVERY study in hospitalized patients. There are no studies or data in using corticosteroids at an early phase of COVID-19 and its impact on disease course and mortality in outpatient setting.

**Subjects & Results:** We retrospectively collected data from 288 COVID-19 patients, treated with oral corticosteroids as soon as the diagnosis was made in outpatient setting. Out of 288 patients treated in four ambulatory clinics (two primary care clinics and two allergy specialty clinics), 275 patients (95.5%) recovered with no complications and hospitalization. Eleven (3.8%) patients were hospitalized. Two out of 11 (0.72%) hospitalized patients deceased secondary to COVID-19 complications. Two patients (0.72%) went home with hospice, as they have terminal illness. Majority of patients (63.5%) started oral steroids within 3 days of onset of symptoms. Significantly lower dose of corticosteroids required in patients treated within 3 days of onset of symptoms vs. after 3 days.

**Conclusion:** Based on this small retrospective study, treatment with oral corticosteroids at early phase of the disease prevented hospitalization (95.5%). There were no deleterious effects of steroids observed when treated during early viral phase of the disease. Prospective and randomized clinical trials are warranted.

**Keywords:** Steroids, COVID-19, Hospitalization, Prevention, Hypoxia, Early Treatment

**Introduction:** Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection emerged as a serious viral illness causing COVID-19 disease and pandemic. It was first reported in China in December 2019 (1). SARS-CoV-2 virus infected over 561 million people worldwide and caused mortality of over 6.3 million as of late June 2022 (2) at the time of submission of this article. New variants of the virus are emerging and causing faster spread and severity of this infection (3). Even though majority of COVID-19 patients are asymptomatic, this infection could cause multitude of signs and symptoms, which include fever, sore throat, cough, fatigue, myalgia, arthralgia, loss of smell and taste, headaches, and severe cases of dyspnea, hemoptysis, and pneumonia (4). Epidemiological studies indicate the time of incubation for COVID-19 was estimated to be an average of 7 days, with a range of 2-11 days (5). In one study from China involving about 80,000 cases, the overall mortality rate was about 0.4–2.0% but increased to up to 50% in immune-compromised patients with comorbidities (6). The primary mechanism of spread of this virus is through the facial and nasal mucosal surfaces, by binding to angiotensin converting enzyme-2 (ACE2) receptors followed by receptor-mediated endocytosis (7). The massive cytokine storm leads to vascular permeability, endothelial dysfunction, and hypercoagulability. These mechanisms collectively result in acute respiratory distress syndrome, arterial and venous thromboembolism, cardiovascular dysfunction, and death (8). Subjects who survived have been shown to develop chronic inflammatory disease like myositis, polyarthropathy, myocarditis, Still's disease, chronic demyelinating polyneuropathy, systemic lupus erythematosus (SLE) and vasculitides. Several inflammatory markers such as procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactic dehydrogenase (LDH), ferritin, and D-dimer are elevated in severe cases of COVID-19 (9).

Based on the known pathophysiology of SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, several therapeutic approaches utilizing immunomodulatory agents like antiviral drugs such as remdesivir, anti-cancer drugs such as selinexor, ruxolitinib, kinase inhibitors, serine protease inhibitors, antimicrobials such as chloroquine, ivermectin, and finally anti-inflammatory agents were studied with variable success in various phases of infection (10). But to date, there is no one effective agent beneficial in COVID-19 patients except corticosteroids. Controlling this inflammatory immune response could be the only first-line readily accessible treatment against COVID-19. Cortico-

steroids were studied in severe COVID 19 hospitalized patients. In a small retrospective study involving 201 severe COVID-19 patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20-0.72 (11). RECOVERY study investigated the role of dexamethasone in hospitalized patients with COVID-19 infection. Patients who received 6 mg of dexamethasone once a day for 10 days had lower 28-day mortality among patients receiving either oxygen alone or mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) (12).

While treating a small group of patients with history of asthma and related hyperactive airway disease, we observed that early intervention with steroids alleviated COVID-19 related symptoms and hospitalization. We treated the SARS-CoV-2 infected asthma patients in early 2020 with prednisone, to alleviate their asthma exacerbations and realized later as due to COVID-19. Early treatment with pulse dose corticosteroids, not only rapidly provided relief of their symptoms, but also prevented hospitalization. Based on our initial observation, we have treated several patients with SARS-CoV-2 infection with moderate to high doses of corticosteroids. Here we report the results of retrospective data analysis involving 288 COVID-19 patients, treated with corticosteroids in early course of their disease.

### **Subjects and Methods:**

**IRB Approval:** The study was approved by the Institutional Review Board of Western Michigan University, Kalamazoo, Michigan.

**Data sources:** We retrospectively collected data on COVID-19 patients, who were treated with corticosteroids, in four ambulatory care clinics in different counties of the United States of America. Data was collected from all charts (n = 288) of patients diagnosed and treated for SARS=CoV-2 infection in one ambulatory clinic each from Genesee, Calhoun counties in Michigan; Limestone County in Alabama; and Cameron County in Texas between March 2020 and January 2021. Demographic, clinical information and laboratory data were extracted from paper charts and electronic medical records (EMR); whichever was available in the clinics. Data were reviewed for all patients treated with steroids to verify the date of (a) first visit, (b) when the clinical symptoms started, (c) recovery, comorbidities and the medications prescribed to treat COVID-19. Patients were included in the analysis if they had confirmed positive nasopharyngeal swab SARS-CoV-2 PCR test result, and/or

positive rapid antigen test for SARS-CoV-2 spike protein. Charts were also reviewed for the patients with a clinical disease, which was confirmed serologically with measurable IgG antibodies to SARS-CoV-2.

**Key Variables of Interest:** Analysis was limited to patients 18 years and older, with clinical and/or laboratory diagnosis of SARS-CoV-2 infection. Patients younger than 18 years, and those with mental disabilities, psychiatric illnesses were not included. We collected data on demographic variables including age, gender, comorbid conditions, home medications, clinical variables including symptoms, vital signs, dose, length, type of corticosteroids, concomitant supportive care medications, laboratory data including complete blood counts, comprehensive metabolic panel, inflammatory marker such as ESR, CRP, procalcitonin, LDH (when available). We also collected data on disease outcomes, including time to recovery of symptoms, complications from treatment and COVID-19 disease, hospitalization and/or death. Primary clinical outcomes of the study include frequency of hospitalization, clinical improvement, time to complete recovery from symptoms and the dose and length of corticosteroids use and need for oxygen support. Secondary outcomes included improvement of laboratory measures, association of recovery with existing comorbidities and medications used to treat COVID-19.

**Statistical Analysis:** Data containing all the demographic and clinical variables (continuous and categorical) were collected and stored in Excel spreadsheets (Microsoft Excel, 2019) and analyzed using SPSS (IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y, USA)) Quantitative data are expressed as the mean ± standard deviation (SD) and nominal data as percentages. Comparisons between groups for quantitative variables were performed using the *t*-test. Nominal variables were evaluated using the  $\chi^2$  test. Statistical data were considered significant at *p* value ≤ 0.05. Comparisons were made with data from the county where the outpatient clinic is located.

**Results:** Of 288 patients with confirmed with COVID-19, 40% were males (n = 115), 60% were females (n = 173). The mean age of the patients in this study was 55.35 years (±SD 17.31), with a body mass index (BMI) of 31.06 (± SD 7.33). The ethnicity of COVID-19 patients includes 65.8% (n = 162) Hispanics, 26.9% (n = 102) Caucasians, 3.2% (n = 13) African Americans, 3.2 % (n = 9) East Indians, and the rest Asians and others (n = 2) (Table 1). In this analysis,

100% of the patients had clinical and/or laboratory-confirmed SARS-CoV-2 infection. The most common comorbidities of these patients are hypertension (42%), diabetes mellitus (25%), asthma (11%), immune deficiency (8%) as shown in Graph 1.

**Table-1: Race and Gender Distribution of 288 COVID-19 Patients Reviewed during the Study Period**

Race	Gender		Total	
	Female	Male	N	%
Hispanic	99	63	162	56.25%
White	59	43	102	35.42%
Black	8	5	13	4.51%
Asian Indian	6	3	9	3.13%
Asian	1	1	2	0.69%
<b>Total</b>	<b>173</b>	<b>115</b>	<b>288</b>	<b>100.00%</b>

Most common symptoms include cough (64%), fever (42%), sore throat (38%), headache (36%), shortness of breath (31%), chills (26%), and fatigue (24%). Most common home medications include antihypertensive drugs (38.2%), statins (33.1%), ACE/ARB inhibitors (30.2%), glycemia control agents (17.5%), and relatively low percentage on anticoagulants (5.1%), immunosuppressant drugs (3%) and oral corticosteroids (2.5%). Dose of the oral steroids adjusted as required for these patients that are on oral steroids at the time of their initial visit. Most patients, 94.4% (n = 272) had seen their healthcare provider within the first week of the onset of their symptoms (Table 2).

**Table 2: Start of Symptoms to 1st Visit to Clinic in Days**

Days from Symptoms to 1st Visit	Gender				Total	
	Female		Male			
	N	%	n	%	N	%
00 - 05	147	84.97	89	77.39	236	81.94
05 - 10	23	13.29	21	18.26	44	15.28
10 - 15	2	1.16	3	2.61	5	1.74
15 - 20	1	0.58	0	0.00	1	0.35
20 & 20+		0.00	2	1.74	2	0.69
<b>Total</b>	<b>173</b>	<b>100.00</b>	<b>115</b>	<b>100.00</b>	<b>288</b>	<b>100.00</b>

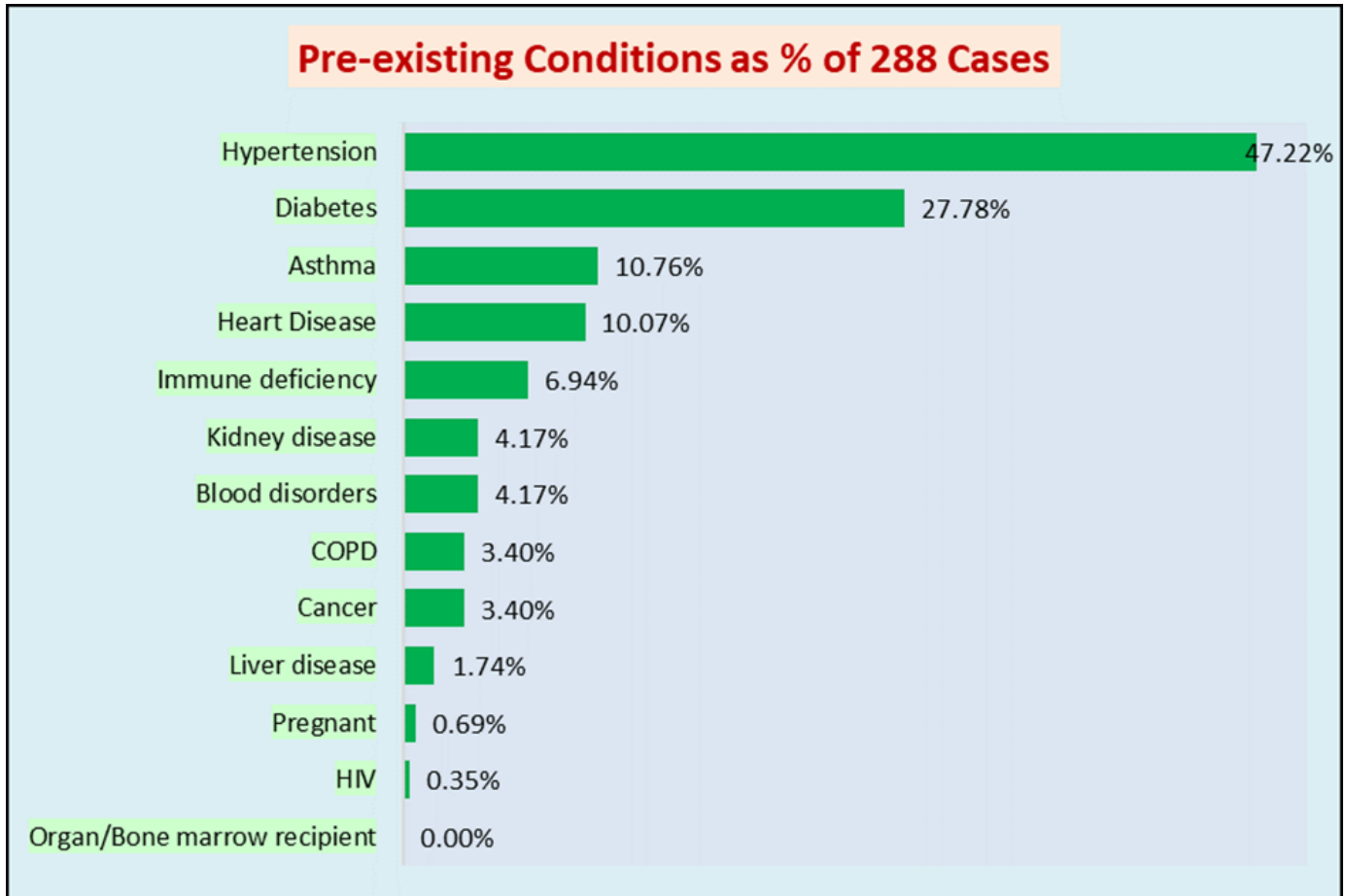
Imaging was done for 18.9% of patients, which include chest X-rays (51/288) and CT scans (19/288). Among patients with chest X-rays, 28 (54.9%) were radiologically positive for COVID-19 disease-related findings in their lungs. For those patients with CT scan, 57.89% of patients (9 out of 19), showed findings consistent with COVID-19 related changes in their lungs. Most patients (284 out of 288 (98.6%)), recovered from their infection. Two (0.7%) patients with history of terminal conditions (Patient 1: 84-

**Table 3: Requirement of Corticosteroid Dose When Started before Third Day Versus After Day Three of Start of Symptoms in milligrams.**

First Symptoms to start of Steroid in days	Values	Gender		Total
		Female	Male	
<= 3 Days	Number of Patients	114	69	183
	Average of Total Drug in mg taken	351.30	344.12	348.62
	Std Dev of Total Drug in mg taken	224.16	179.25	208.54
> 3 Days	Number of Patients	59	46	105
	Average of Total Drug in mg taken	509.31	562.50	532.84
	Std Dev of Total drug in mg taken	393.42	521.23	455.18
<b>Total</b>	<b>Number of Patients</b>	<b>173</b>	<b>115</b>	<b>288</b>

year male with metastatic prostate cancer, diabetes mellitus, obesity, and cardiovascular disease; Patient 2: 81-year female with BMI of 33 with metastatic breast carcinoma and severe dementia) went home with hospice and later deceased. The families of these two patients requested hospice with no further intensive medical treatment or hospital admission. Two (0.7%) patients died from COVID-19 related complications. Only 11 patients (3.8%) were hospitalized, out of which one patient was admitted to the intensive care unit (ICU) (0.36%) 2 patients (0.72%) died from COVID-19 related complications.

**Graph 1: Pre-existing Conditions of 288 COVID-19 Patients Reviewed during the Study Period**



One hundred and eighty-three (63.5%) patients were started on the corticosteroids within the first 3 days of onset of symptoms, whereas remaining 105 patients received after the third day of onset of symptoms. One hundred and ninety-nine (69.1%) patients received of

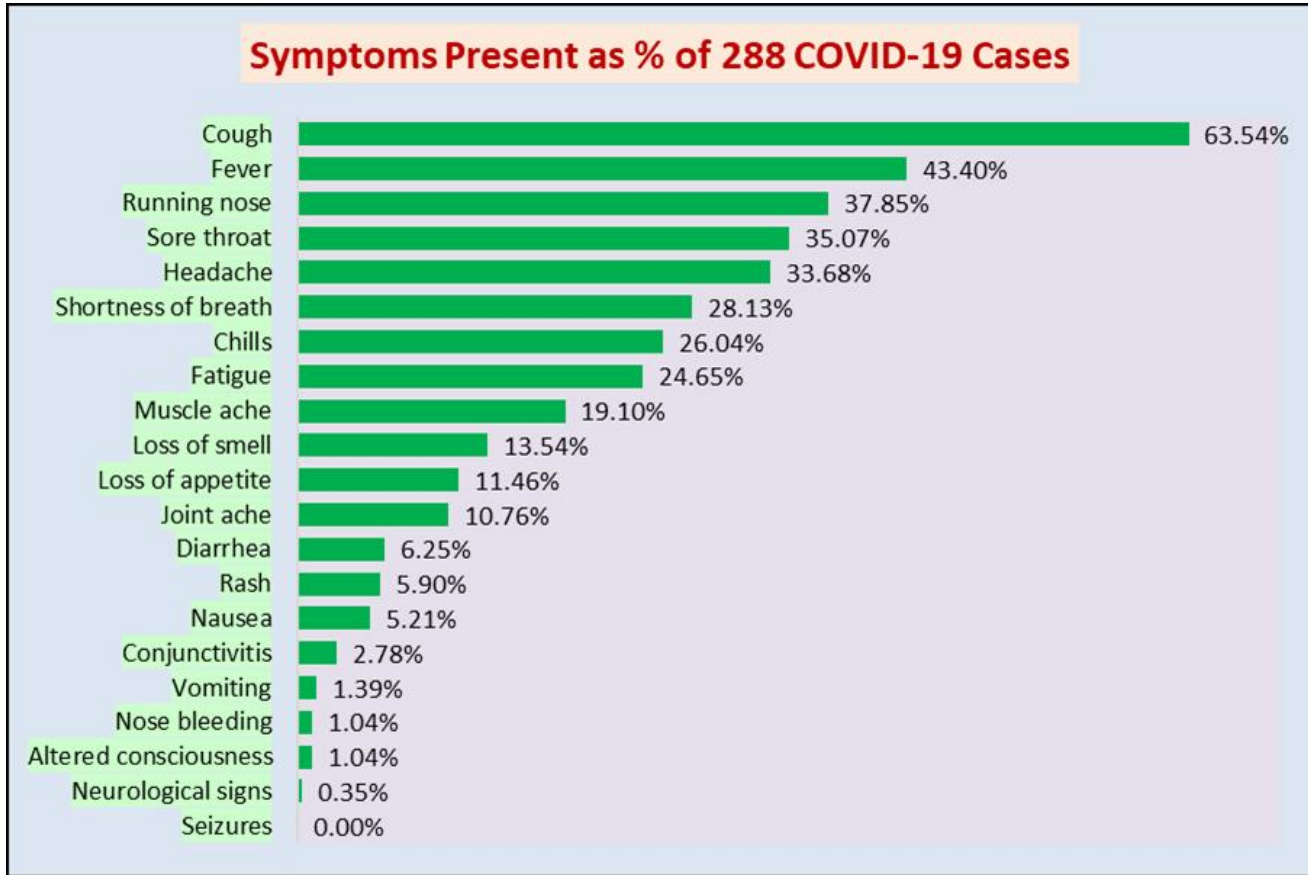
steroids for  $\leq 10$  days, with an average dose of  $348.62 \pm 208.54$  mg of methyl prednisone or steroid equivalent. The dose of corticosteroids was higher when started after third day of onset of symptoms  $532.84 \pm 455.18$  mg,  $n = 105$  (Table 3). Of the 288 patients, 197 had oxygen saturation



(SpO<sub>2</sub>) 95% or above throughout the treatment period, while in 51 patients had SpO<sub>2</sub> between 94 - 90%; in 5 patients SpO<sub>2</sub> was between 89 - 85%, and in 6 patients SpO<sub>2</sub> was <85% at some point of treatment. SpO<sub>2</sub> readings

were not available for 29 patients. Various laboratory parameters that indicate the degree of inflammation and thus the disease severity were evaluated. These included the mean D-dimer, LDH, and CRP levels.

**Graph 2: Presenting symptoms of 288 COVID-19 Patients**



**Discussion:** Our small study involved 288 SARS-CoV-2 infected patients with mild to moderate symptoms, who were safely treated with steroids in an outpatient setting. Majority of these patients recovered, and hospitalization rate is low (3.8%). We also noted that patients when treated with steroids within 3 days of onset of symptoms required less amount of steroids, compared to those treated after 3 days of onset of symptoms (Table 3). To the best of our knowledge this is first reported study of COVID-19 patients, treated with steroids in the outpatient setting. Use of steroids in COVID-19 patients with mild to moderate symptoms is not clear and was not studied before.

Recent data in critically ill hospitalized patients with COVID-19 infection and acute respiratory failure, corticosteroid therapy improved morbidity and mortality outcomes. Outcomes were same, weather they used

dexamethasone (12-14) or hydrocortisone (15-16). Tomazini et al, in a Brazilian multicenter, randomized, open-label, clinical trial involving 299 adults with moderate or severe ARDS due to COVID-19 showed that 144 patients who received dexamethasone treatment plus the standard treatment had significant increase in the number of days without mechanical ventilation during the first 28 days (13). Similarly, Villar et al published a multicenter randomized clinical trial and showed that early administration of dexamethasone in COVID-19 patients who had moderate and severe ARDS has an increased average number of days without mechanical ventilation and reduced mortality compared to the control group (14). WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group conducted a meta-analysis, which concluded that early systemic corticosteroid intervention was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19 (17). The RECOVERY study (12) is the first

randomized clinical trial that showed the benefit of corticosteroids, in reducing mortality from SARS Cov-2 induced inflammatory response, even at low doses (6 mg dexamethasone for 10 days). It is important to acknowledge the benefit and the definitive change this study brought to include corticosteroids in every protocol to treat COVID 19 worldwide. Edalatfard et al also conducted randomized trial involving 68 patients with severe COVID-19 infections with respiratory symptoms (18). They used intravenous methylprednisolone pulse dose of 250 mg/day for 3 days vs. standard of care. They showed improved clinical recovery (94.1% vs. 57.1%) and decreased mortality rate in the methylprednisolone group (5.9% vs. 42.9%;  $p < 0.001$ ) compared to standard of care group.

In early period of COVID-19 epidemic/pandemic, we noticed that patients presenting with acute exacerbation of asthma due to acute viral illness responding quickly and recovering completely when treated with 1-2 mg per kg body weight per day of prednisone for 1-2 weeks. Studying these patients retrospectively we recognized that the exacerbation of asthma is due to SARS-CoV-2 infection. This led to the treatment of subsequent patients with COVID-19 infection with oral corticosteroids when they presented to our ambulatory care centers with clinical symptoms of COVID-19. Our results showed that we could prevent the progression of the disease and prevent hospitalization of most patients. In our sample of 288 patients analyzed in the ambulatory clinics who presented with COVID-19 and were treated with oral corticosteroids (0.5 to 2 mg/Kg body weight methylprednisolone or an equivalent corticosteroid). About 98.6% of these patients were completely recovered from COVID-19 in 3 to 15 days with rapid relief of symptoms and normalizing the laboratory studies and avoided hospital admission. We saw no worsening of their general condition or comorbidities. Our study outcomes showed no difference regarding patient oxygenation status before the treatment with corticosteroids. This contrasts with RECOVERY study, where maximal benefit was found in patients with hypoxemia. The treatment with corticosteroids was continued until all the inflammatory markers returned to normal, extending, if necessary, to more than three weeks. The hospitalization rate was less than 5% and mortality is significantly low (1.4%). This contrasts with the data collected in the respective counties, individually and collectively. (Hospitalization 15-20% and mortality is 3.5 - 6.5%. (Data obtained from the respective counties where the clinics are situated).

Previous studies, utilizing steroids in critically ill patients with influenza (H1N1) or MERS showed negative impact in clinical outcomes (18-20). They reported that steroids might slow the clearing of viral RNA. Tang et al recently published a study from China, that high dose steroids (methyl prednisolone) could slow the clearance of COVID-19 RNA. But this study was terminated early because of decline in the frequency and hospitalization of COVID-19 patients (21). In contrast, Spagnuolo et al reported that SARS-CoV-2 clearance was associated with age and severity of disease, rather than early use of steroids (22). In our study of the 288 patients, we have found no clinically or biologically significant deleterious effect on the disease progress, morbidity, or mortality of COVID-19 in patients treated with corticosteroids early in the course of the disease. Therefore, we presume that the rate of viral clearance has no significance in the recovery of patients from COVID-19 and the delayed clearance of SARS-CoV-2 virus does not result in increased morbidity and mortality of this disease. The latter may be mainly related to the uncontrolled immune response of the host.

The pathogenesis of severe pulmonary and other organ injury related to COVID-19 is not due to direct viral infection and is due to an increase in inflammatory cells and release of sustained amounts of the pro-inflammatory cytokines, which in turn causes excessive adhesion molecule expression on endothelial cells and platelet aggregation. The resulting microvascular thrombosis leads to vascular leak, tissue necrosis and organ failure (23). Unfortunately, many drugs used to control the hyperinflammation in the chronic autoimmune disorders failed to relieve the extensive multi-organ inflammation in COVID-19 disease and have no significant impact in preventing morbidity and mortality. The effectiveness of hyperimmune plasma, JAK-inhibition, anti-cytokine antibody treatments was tried with the most minimal effect on mortality (8, 10). We believe that early treatment with corticosteroids have a role in preventing the cytokine storm and thereby improving morbidity and mortality.

The most significant finding from our observations is that hospitalizations were markedly decreased (3.8%,  $n = 11$ , hospitalized) by treating with corticosteroids early in the course of the disease probably by preventing the inflammatory phase. We believe that our small retrospective study is hypothesis generating. Since there were no adverse effects or worsening of the COVID-19 severity, even when the patients were treated during their early viral phase, large studies in the double-blind

randomized setting would be provide more insights. Early intervention studies in COVID 19 patients, with steroids and/or combined with other immune modulating agents are warranted and they will potentially guide physicians across the globe to prevent costly hospitalizations and decrease financial burden and toxicity, especially for developing countries.

**Limitations of the Study:** Despite the compelling positive outcomes with early use of oral corticosteroids in patients with COVID-19 infection, there are several potential limitations in our study. First, 4 physicians at 4 communities treated all the patients in this study, creating potential sampling bias, which may affect the evaluation of the role of corticosteroids. Second, we only focused on the effect of corticosteroids on hospitalization rates. There is no standardization of type of steroid, dosage, and duration of treatment in our patients. Oral steroid dose is based on individual physician preference, which is based on severity of symptoms, signs, and laboratory data, which could potentially introduce subjectivity and judgment bias. All the consecutive COVID-19 patients were treated with early steroids, therefore there is little room for selection bias. Patients who were hospitalized from the clinic with severe symptoms were not included in this study. Another potential problem is sample size. Despite the small sample size, results from this retrospective study are positive and encouraging, confirmation of these findings in future prospective studies would be highly desirable.

**Conclusion:** As we are pondering and searching for the right answers and waiting for the proper treatment regimen and/or waiting for mass vaccination to attain herd immunity for COVID-19, immunosuppression may be the answer to prevent mortality. Corticosteroids are safe in treating COVID-19 and are inexpensive drugs widely available all over the world. Our observation in this small retrospective study provides evidence that these drugs are safe, effective and with no significant risk of viral spread even when they were used during the viral phase of the COVID-19. It may also block the onset of the hyperinflammatory phase if used early in the treatment. We predict that immunosuppression, especially with corticosteroids, play a major role and the earlier the treatment with corticosteroids started, better will be outcomes in preventing morbidity and mortality. By addressing the inflammation in the earlier stages may also help to prevent the post-COVID-19 sequelae.

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## Review Article

# Personalized and Predictive Preventive Health Screening: A Continuum of Wellness

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**Abstract:** Good health is a core determinant of quality of life (QOL) and impacts an individual's ability to live a happy and fulfilling life. Although reductions in mortality rates have caused life expectancy to increase rapidly, this improvement is not proportional to the trajectory for *healthy* life expectancy owing to non-communicable diseases (NCDs)-induced *multi-morbidity* and disability. The WHO estimates that NCDs cause approximately 41 million deaths worldwide, with 15 million being between 30 and 69 years. Most of these "*premature*" deaths occur in low- and middle-income countries. Prospective studies project that NCD incidence and prevalence will escalate substantially as the population aged 60 and over increases. Screening, detection, contemporaneous monitoring of disease progression, and timely intervention are vital determinants for clinical care management of NCDs. The timely and systematic implementation of detection and screening modalities for NCDs is pivotal for curbing multi-morbidity and mortality, reducing pharmaco-economic burden, and improving QOL. This article highlights how it is possible to integrate personalized screening and disease risk prediction to individualize management protocols and monitor health outcomes with a structured continuum of care.

**Key Words:** Non-communicable diseases (NCDs), QOL, Screening, Personalized, Risk Score, Care Continuum

**Health is a Key Pillar of Quality of Life (QOL):** QOL is an important multidimensional concept encompassing a cumulative subjective evaluation of life from positive and negative domains. Along with inter-related factors such as core values, education, employment, and socioeconomics, health is also a pivotal domain of QOL. We should evaluate population health not merely using mortality and morbidity assessments but with a multi-pronged approach that includes physical, mental, and social domains. With advancements in medical and public health, health outcomes are assessing overall population health based on reduced mortality and improvements in QOL (1). Although "nature" (genetics) is an intrinsic determinant of health, "nurture" (attitude to life and lifestyle) also plays a vital role in the symbiosis of health and happiness (2). Correlates of health related QOL include risk factors for chronic conditions, mental health perceptions (e.g., energy level, mood), functional status, social support, and socioeconomic status (1).

### **We are Living Longer, but are We Healthy and Happy?**

According to estimates from the World Health Organization (WHO), global human life expectancy has been increasing rapidly, primarily due to improved medical care, better hygiene, adequate food and hydration, and a decline in mortality rates. Between 2000 and 2019, life expectancy increased globally by more than six years (from 66.8 years in 2000 to 73.4 years in 2019). However, this trend in longevity reflected an interesting fact. The increase in healthy life expectancy or the average number of years lived in good health (5.4 years) did not keep pace with the rise in life expectancy (6.6 years). Epidemiologists attributed this observation to the fact that *despite a decline in mortality rate, multi-morbidity* (related to age, gender, body constitution, family history, lifestyle, environment, occupation, disability, or a confluence of all these factors) continued to be prevalent (3-6).

General global life expectancy is increasing at a rate greater than healthy life expectancy, with an expansion in the trajectory of multi-morbidity (average number of years lived in poor health). The burgeoning onset and progression of non-communicable diseases (NCDs) are the underlying cause of this multi-morbidity (3-8).

The WHO estimates that NCDs cause approximately 41 million deaths worldwide, with 15 million in the age range of 30 and 69 years. Low- and middle-income countries account for a higher burden of NCDs and *premature mortality* (deaths before age 70). Prospective studies project that NCD incidence and prevalence will escalate substantially as the population aged 60 and above increases. Based on data from a 2014 WHO global status report, NCDs contribute to around 5.87 million (60%) of all deaths in India. The four NCD groups mainly responsible for the total NCD mortality and morbidity are cardiovascular diseases, diabetes, chronic respiratory disease, and cancers, contributing to approximately 80% of all NCD deaths (6-9). The key factors driving this increased NCD prevalence are physical inactivity, unhealthy diets (a low proportion of fruits, vegetables, and whole grains, but high quantities of salt, sugar, fat, and processed food), tobacco use (smoking, second-hand smoke, smokeless tobacco), alcoholism, stress, poor sleep patterns, and environmental pollution (6).

The onset and progression of NCDs may vary due to differences in genetics, gender, physiology, social economics, and behavior. Clinical risk factors (hypertension, obesity, high cholesterol, and family history of diabetes or cardiovascular disease) and socioeconomic and behavioral factors (extent of physical activity, alcohol consumption, diet, and smoking) determine NCD onset and progression (6-10).

We need to leverage resources to address this chronic multi-morbidity actively and escalate the rate of increase in healthy life expectancy, which would make a positive foray into optimizing our QOL.

**Preventive Health Screening:** Screening, detection, contemporaneous monitoring of disease progression, and timely intervention are vital determinants for the clinical care management of NCDs, including curbing multi-morbidity and mortality, reducing pharmaco-economic burden, and improving QOL (6).

Preventive health screening helps detect the early onset of chronic diseases in asymptomatic at-risk individuals to mitigate potential progression (including complications) and initiate appropriate lifestyle and diet modifications, regular monitoring, and safe and efficacious pharmacological interventions (6, 11).

Although physicians usually prefer annual preventive health screening, some may recommend a bi-annual frequency for those with risk factors. Basic preventive health screening for individuals between 18-40 years should include:

- Basic diagnostic tests for cardio-metabolic functions (ECG, lipid profile, blood glucose, kidney function, liver function, thyroid function)
- Imaging tests for lungs and abdomen
- Basic cancer screening:
  - Prostate cancer (PSA) for men
  - Breast (mammogram or USG) and cervical (Pap Smear) for women
- Physician consultations
- Diet and lifestyle modification counselling

Even though screening tests are not precisely "diagnostic" or 100% accurate in all cases, they play an essential role in identifying population subsets for whom additional testing will determine the presence or absence of pathophysiology while minimizing ambiguous or confusing results (11).

**Management of even one chronic disease can drive improvements in other clinical domains. Here are some examples:**

- The UK Prospective Diabetes Study (UKPDS) was a 20-year (from 1977 to 1997) long, randomized, multicentric (23 clinical sites) trial involving 5,102 individuals with newly diagnosed type 2 diabetes. This landmark trial demonstrated that we could reduce diabetes-related complications by improving glycemic and blood pressure control compared with conventional diet therapy alone. Intensive glucose control resulted in a 25% risk reduction for microvascular disease, a 12% risk reduction for any diabetes-related endpoint, and a 16% reduction in the risk of myocardial infarction (12, 13).
- In a meta-analysis (123 studies; 613,815 participants) published in *The Lancet* in 2016, every 10 mm Hg systolic blood pressure lowering led to a significant risk reduction for major cardiovascular disease events (relative risk [RR] 0.80, 95% CI 0.77-0.83), coronary heart disease (0.83, 0.78-0.88), stroke (0.73, 0.68-0.77), and heart failure (0.72, 0.67-0.78). These clinical improvements cumulatively resulted in a significant 13% reduction in all-cause mortality (0.87, 0.84-0.91) (14).
- An analysis of weight loss and risk reduction of obesity-related outcomes in 0.5 million people (age  $\geq 18$  years; BMI = 25.0–50.0 kg/m<sup>2</sup>) from a UK primary care database indicated that a median 13% weight loss resulted in risk reductions for diabetes (41%), sleep apnea (40%), hypertension (22%), dyslipidemia (19%) and asthma (18%) (15).

Therefore, timely intervention for even one chronic medical condition can induce positive clinical outcomes for coexisting comorbidities.

**Table 1: Risk factors that signal a requirement for screening for NCDs [Diabetes, Cardiovascular Disease, Cancer, COPD]**

Risk Factors	NCD to Screen for	Screening Tests
<ul style="list-style-type: none"> <li>Overweight or Obese                             <ul style="list-style-type: none"> <li>Body mass index (BMI): <math>\geq 25</math></li> <li>Waist measurement: 94cm (about 37 inches) or more for males, or 80cm (about 31.5 inches) or more for females</li> </ul> </li> <li>Hypertension (<math>\geq 140/90</math> mm Hg)</li> <li>Dyslipidemia</li> <li>Diabetes</li> <li>Inconsistent physical activity</li> <li>Tobacco intake in any form (smoking, second-hand smoke, smokeless tobacco)</li> <li>Have a father or brother diagnosed with heart disease before 55 years of age</li> <li>Have a mother or sister diagnosed with heart disease before 65 years of age</li> </ul>	<b>Cardiovascular Disease</b>	<ul style="list-style-type: none"> <li>Check lipid levels</li> <li>Electrocardiography (ECG)</li> </ul> <p><u>Additional tests (if required) to confirm the diagnosis:</u></p> <ul style="list-style-type: none"> <li>Echocardiography (ECHO)</li> <li>Angiography</li> </ul>
<ul style="list-style-type: none"> <li>Overweight or obese                             <ul style="list-style-type: none"> <li>Body mass index (BMI): <math>\geq 25</math></li> <li>Waist measurement: 94cm (about 37 inches) or more for males, or 80cm (about 31.5 inches) or more for females</li> </ul> </li> <li>Age: <math>\geq 45</math> years</li> <li>A parent or sibling with diabetes</li> <li>Frequency of physical activity less than thrice a week</li> <li>A history of diabetes during pregnancy or have given birth to a baby who weighed over 4 Kg.</li> <li>Hypertension (<math>\geq 140/90</math> mm Hg)</li> <li>Dyslipidemia</li> <li>Fatty liver disease</li> </ul>	<b>Diabetes</b>	<ul style="list-style-type: none"> <li>Plasma glucose</li> <li>Glycosylated hemoglobin (HbA1C)</li> <li>Urinalysis</li> </ul>
<ul style="list-style-type: none"> <li>Smoker</li> <li>Exposure to air pollution</li> <li>Breathing in second-hand smoke</li> <li>Regular work with chemicals, dust and fumes</li> <li>The genetic condition Alpha-1 deficiency</li> <li>A history of childhood respiratory infections</li> </ul>	<b>Pulmonary Disease</b> COPD, Asthma, Interstitial fibrosis, Pulmonary vascular disease	<ul style="list-style-type: none"> <li>Chest X-ray</li> <li>Spirometry                             <ul style="list-style-type: none"> <li>FEV1</li> <li>FEV1/FVC</li> </ul> </li> </ul> <p><u>Advanced tests:</u></p> <ul style="list-style-type: none"> <li>CT scan</li> </ul>
<ul style="list-style-type: none"> <li>Tobacco use</li> <li>Obesity</li> <li>Regular consumption of alcohol</li> <li>History of infection with certain viruses, such as the human papillomavirus (HPV)</li> <li>Regularly exposed to radiation</li> <li>Regularly exposed to these chemicals: asbestos, nickel, cadmium, radon, vinyl chloride, benzidine, benzene</li> <li>Parents or siblings with cancer or a history of cancer</li> </ul>	<b>Cancer</b>	<ul style="list-style-type: none"> <li>Blood tests</li> <li>X-ray</li> <li>USG</li> <li>Mammogram</li> <li>Pap smear</li> <li>Colonoscopy</li> <li><u>Advanced Tests:</u> <ul style="list-style-type: none"> <li>CT, MRI</li> <li>PET scan</li> <li>Bone scan</li> <li>Radionuclide imaging</li> <li>Biopsies</li> </ul> </li> </ul>

Figure 1: Apollo ProHealth: A Customized Program for Impactful Change

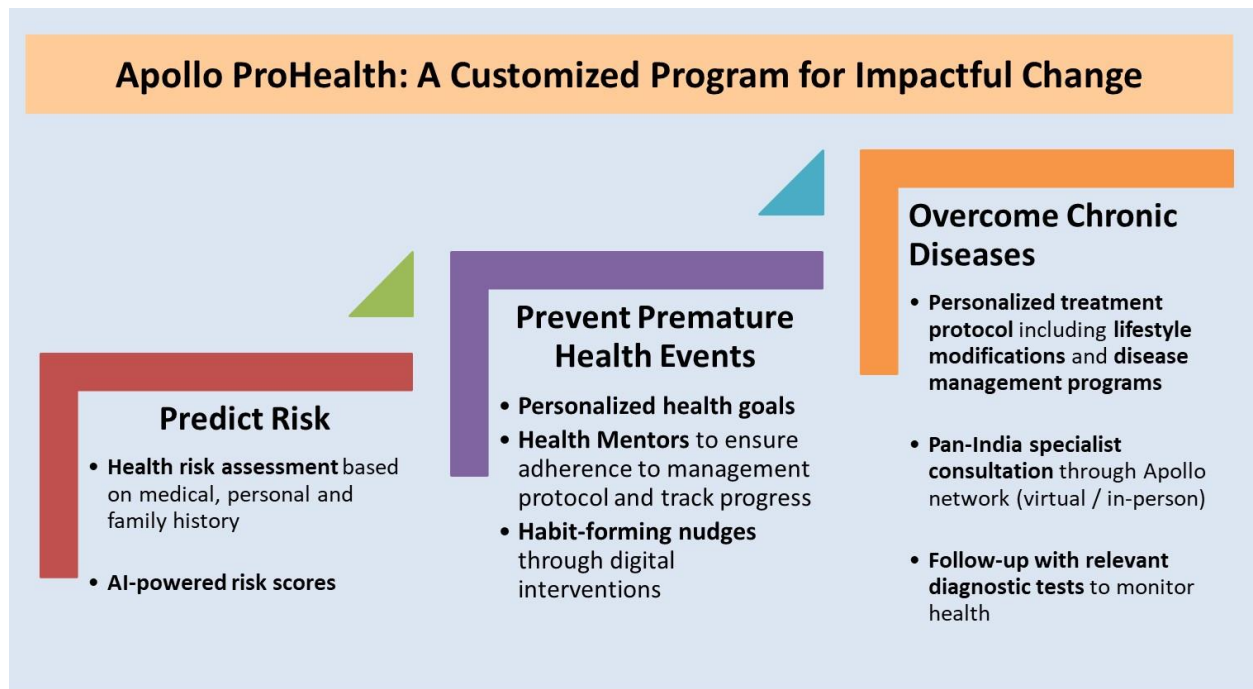


Table 2: AI risk prediction tools and the parameters they assess (Apollo Hospitals Preventive Health. ProHealth - Data on File.)

AI risk prediction tool	What risk does it predict?	What parameters does it assess?
Cardiac risk score (AI-CVD)	Coronary Artery Disease (CAD) - related events in the next 10 years	<p><b>Physical attributes:</b> Height, weight, BMI, psychosocial stress</p> <p><b>Heart health attributes:</b> Heart rate, BP, respiratory rate, pulse rhythm, symptoms (e.g., chest pain, shortness of breath)</p> <p><b>Lifestyle:</b> Diet, alcohol, tobacco, physical activity</p> <p><b>Medical history:</b> Diabetes, hypertension, dyslipidemia, history of heart disease, family history of heart disease</p>
Prediabetes risk score (AI-Prediabetes)	Prediabetes within 3 years	<p><b>Patient parameters:</b> Age, gender, height, weight, BMI</p> <p><b>Medical history:</b> Past medical history, hypertension, symptoms</p> <p><b>Lifestyle:</b> Diet, alcohol, physical activity</p> <p><b>Additional information:</b> Weight circumference, change in body weight in the past 6 months</p>
COPD risk score (AI-COPD)	An acute exacerbation of COPD in the next 3 months	<p><b>Past history:</b> Allergies, cardiac or pulmonary disease, medications, COVID-19 vaccination, influenza vaccination, tobacco intake (including smoking)</p> <p><b>Other questions:</b></p> <ul style="list-style-type: none"> <li>Air quality index of the city of current residence</li> <li>Any breathlessness at rest or activity?</li> <li>Any cough with sputum production?</li> <li>Respiratory rate</li> <li>Any recent increase in pulse rate from baseline?</li> <li>Oxygen saturation</li> <li>Any wheezing on auscultation?</li> </ul>



Figure 2: AI-CVD Risk Score (Reference 30)

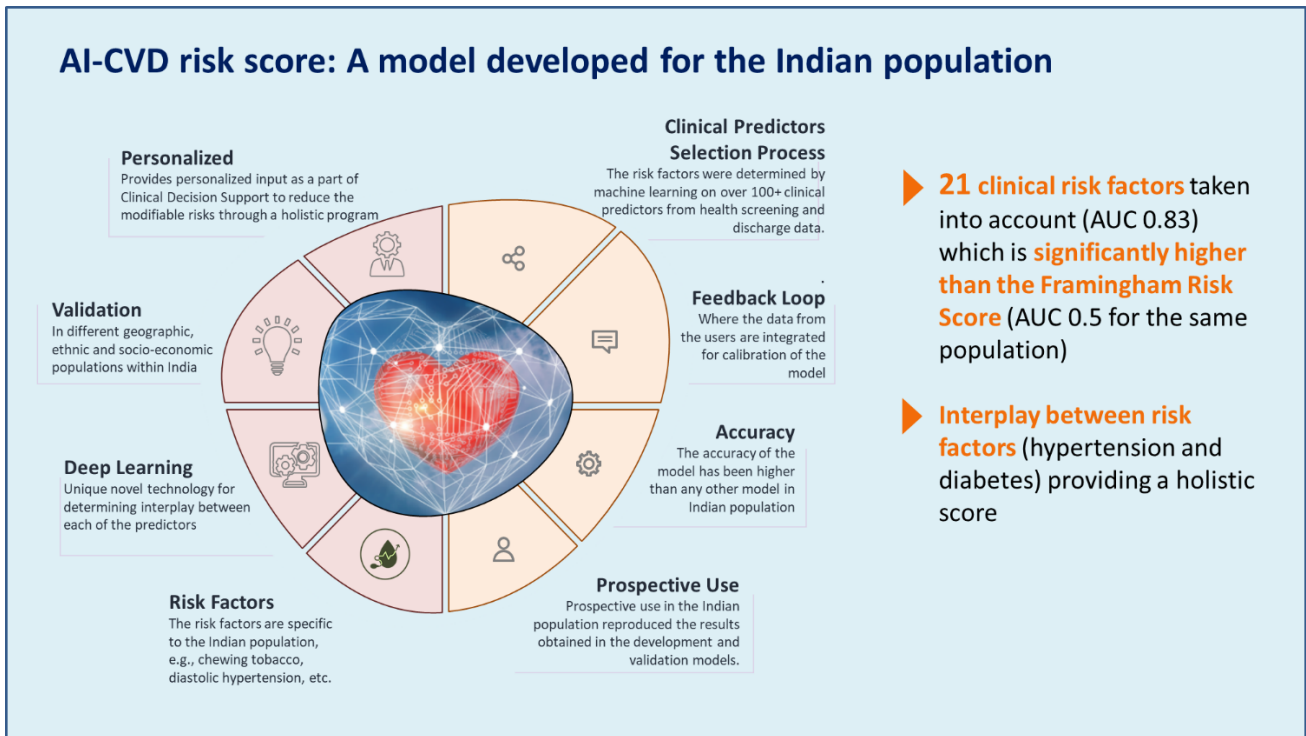
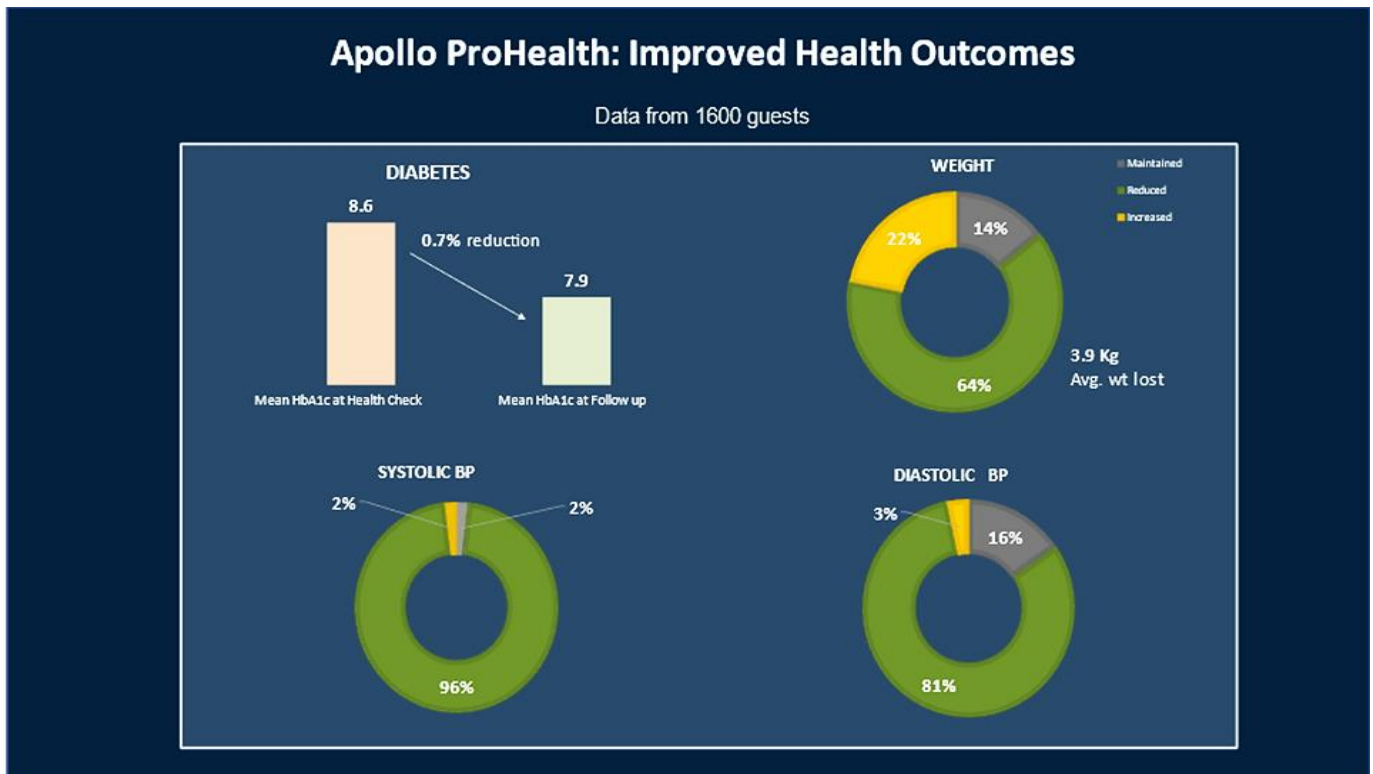


Figure 3. ProHealth Program: Improvement in Health Outcomes with Personalized Recommendations and a Structured Care Continuum (Reference 31)



**Why should Health Screening be “Personalized”?** Personalized screening assessments optimize “person-specific” outcomes and facilitate improved decision-making regarding clinical evaluation and management (16). Parameters considered when personalizing or individualizing screening include gender, age, lifestyle and personal history, medical history (including acute illnesses or comorbidities), and family history. These intrinsic factors impact the risk of disease onset and progression, including the rationale and timing of evidence-based interventions. For example, a personalized screening panel for women  $\geq 45$  years could include:

- Basic diagnostic tests for cardio-metabolic functions (ECG, lipid profile, blood glucose, kidney function, liver function, thyroid function)
- Imaging tests for lungs and abdomen
- Clinical consultation with a physician
- Clinical consultation with a gynecologist to detect risk, onset, or progression of peri- and post-menopausal gynecological disorders
- Pap smear to detect cervical cancer
- A mammogram to detect signs of breast cancer
- A DEXA scan to assess bone mineral density, including FRAX to detect a 10-year probability of osteoporotic fracture

Physicians can assess the interplay of risk factors based on an individual's gender, age, lifestyle, personal history, medical history, and family history to determine whether screening for chronic conditions is required. Table 1 highlights risk factors to prompt **personalized** screening for NCDs (17-23).

**Can we Predict and Score Health Risks?** The advent of digitalization in the biomedical sphere has launched research into quantitative prediction tools. These can help forecast disease onset, its clinical course, prognosis, and the probability of successful response to specific pharmacotherapeutic options. Some models also augment traditional health predictors with genomic and psychosocial data. The tools can guide: a) clinicians to individualize prevention and treatment plans, b) individuals to make more informed decisions regarding prevention regimens, and c) healthcare systems to allocate personnel and other resources to patients most at risk for an outcome (risk-stratification) (24).

Data-driven prediction models or “risk calculators” have been used successfully in the clinical domain and typically employ information readily available to health professionals, such as demographics and medical factors assessed during clinical consults. Prediction models combine the available risk factor data into a single index, usually called a *risk score*, which conveys information about the probability of experiencing a health

outcome, e.g., the incidence of a disease that the physician has not yet diagnosed. Risk prediction models typically undergo multiple validation cycles and revisions within samples of their target population before successful use in clinical settings (24, 25). One of the most widely used validated prediction models, the Framingham Risk Score (FRS; <http://www.cvriskcalculator.com/>), generates a probability of a cardiovascular outcome such as myocardial infarction or stroke in the next ten years based on the input of cardiovascular factor data such as demographics, smoking or obesity. The score subsequently guides management recommendations from the American College of Cardiology and American Heart Association (e.g., initiation of statin therapy for a risk score  $> 7.5\%$  for stroke or myocardial infarction in the next ten years in the 40–75 years group) (26). Another interesting data-driven prediction model is the Fracture Risk Assessment Tool (FRAX®). FRAX® algorithms, developed from evaluating population-based cohorts from Europe, North America, Asia, and Australia, give the 10-year probability of a major osteoporotic fracture (spine, forearm, hip or shoulder fracture) (27).

**Apollo ProHealth: An Artificial Intelligence (AI)-Powered Personalized Preventive Health Program:** Can we combine a personalized health screening program with individualized risk prediction assessments to guide the evaluation of disease onset and severity progression, targeted intervention, and response to treatment? Can such a program provide a “continuum” of care and wellness long-term? Is it possible to regard such a program as a *journey* to sustain a satisfying QOL?

Apollo ProHealth, launched by Apollo Hospitals Enterprise Ltd. in India, integrates personalized preventive health screening, predictive risk scores and clinical evaluations, facilitating targeted intervention, a continuum of care, and a proactive path to wellness. The program design is developed based on data from approximately 25 million health screening assessments across the Apollo Hospitals ecosystem (Apollo Hospitals Preventive Health. ProHealth 2021. Data on File.). The ProHealth platform has three pillars (Figure 1).

#### **Risk prediction:**

- Health risk assessment based on demographics, personal, medical, and family history that will guide health screening recommendations, follow-up tests and consultations
- AI-powered risk scores to predict clinical outcomes based on current health status and medical or family history

#### **Preventing Premature Health Events**

- A personalized health management protocol including lifestyle modifications (e.g., diet and nutrition, physical activity,

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sleep hygiene, stress management, tobacco, and alcohol avoidance)

- Physician consultations and follow-up assessments to monitor the health status

### Overcoming Chronic Diseases

- **A structured, personalized care continuum that ensures one stays on track as per health goals set by the physician**

- o A dedicated health mentor will proactively work with the individual (e.g., phone calls at regular intervals) to ensure adherence to the management protocol and recommendations (diet, physical activity, stress management, clinical consults, follow-up tests). The health mentor will also track their progress and provide guidance, if needed, regarding booking follow-up tests and physician consultations.

- o Digital interventions (app, messages, emails) to facilitate seamless monitoring of progress and navigation of personal health records, appointment booking, and customized tips for health and lifestyle management

- o Persons diagnosed with chronic disease(s) will receive messages at 3-4 monthly intervals about various topics, including disease awareness, stages of the disease, clinical relevance of tests, reminders, and feedback, etc. The content and frequency of message delivery will sometimes depend on disease severity (mild, moderate, or severe).

**AI-powered Risk Scoring Algorithms** are increasingly used in clinical settings to improve evidence-based clinical decision support, health outcomes, patient experiences, and insights for biomedical research. AI is gaining momentum in personalized disease detection and management, informed patient care, efficient administrative and clinical workflows, reduced care costs, and enhanced physician-patient engagement (28, 29).

**A Key Dimension of Apollo ProHealth is its AI-powered Risk Assessment.** Apollo ProHealth has implemented predictive risk scoring for cardiovascular disease, prediabetes, and chronic pulmonary disease, with ongoing risk scoring algorithm development for many more chronic conditions. These AI-driven risk prediction tools compile data based on various parameters, such as age, gender, diet and lifestyle, medical history, and family history, to generate a score predicting mild, moderate, or high risk. These tools also have integrated clinician decision support guides (Apollo Hospitals Preventive Health. ProHealth 2021. Data on File.). These comprehensive, community-based risk assessment tools have been developed based on Indian demographics and validated by multiple national and international institutions (Table 2). Figure 2 highlights features of

the AI-CVD or the cardiovascular disease risk scoring model (30). The AI-based CVD risk score, which predicts the risk of CVD events (e.g., Acute MI / ACS) in the next ten years, was developed based on data from 31,599 participants (age 18-91 years) in six Apollo Hospitals from 2010-2017. A multi-step selection process using Spearman correlation coefficient and propensity score matching yielded 21 risk factors, which via a Deep Learning Hazard Model, could predict event occurrence and timing. When they compared accuracy and precision of prediction for the AICVD vs conventional risk scores (Framingham Heart Risk score [FHRS] and QRisk3), AICVD demonstrated a superior Positive Likelihood Ratio (AICVD–6.16 to FHRS– 2.24 and QRisk3– 1.16) and accuracy (AICVD– 80.15% to FHRS–59.71% and QRisk3– 51.57%). The AI medical team validated this tool with independent retrospective cohorts of participants from India and the Netherlands.

The Apollo Hospitals Group has recently received the coveted ISO 13485:2016 British Standards Institution (BSI) quality certification for its AI-based clinical applications. This certification validates an ongoing commitment to adopting the highest quality management standards in developing and deploying clinical AI programs.

With an evidence-based structured, personalized preventive health screening, management protocol and long-term care continuum, individuals observe improved health outcomes in the months ahead. Figure 3 highlights positive health outcomes because of the ProHealth program (31).

**ProHealth DeepX: Making Preventive Health Tangible:** We often ignore our health until we become symptomatic. We need to make health tangible to help people understand the potential onset and progression of pathophysiological processes in their bodies and motivate them to action. In partnership with Microsoft, Apollo Hospitals has helped visualize our heart health via an immersive mixed reality experience with **ProHealth DeepX** (Apollo Hospitals Preventive Health. ProHealth 2021. Data on File.). By using Microsoft HoloLens, we can view how healthy our cardiovascular system is and what can happen to the heart if we make the necessary lifestyle shifts. Once individuals enter data about their physical attributes, heart health, lifestyle, and medical history, they receive a cardiac risk score and can visualize a 3D image of a heart and artery. A 3D mixed reality visualization coupled with audio narratives provides insight into normal physiology and pathological changes driving the onset and progression of coronary heart disease, personalized to their modifiable risk factors, such as hypertension, diabetes, and dyslipidemia. Finally, the program suggests a set of personalized recommendations, including lifestyle and dietary modifications, maintaining a healthy BMI, monitoring, and maintaining glycemic and

blood pressure control, stress management, follow-up tests, consultations, and referrals.

**Additional Facets of ProHealth:** Disease awareness and preventive screening for early detection are pivotal to ensuring safe and effective, individualized clinical management. As part of the ProHealth initiative, we aim to continually update our guests with relevant medical information about various preventive health domains via our ProHealth website and social media. We periodically conduct camps in the non-metro or suburban areas to impart knowledge on disease state awareness and prevention, including training for healthcare workers and care continuum health mentors. ProHealth has also started a network of buses providing mobile point-of-care personalized screening for ProHealth guests with a remote location as a barrier. Another novel dimension of the program is a web and phone-based application called "Camp App." This application, launched in May this year, captures guest data at health camps, including vitals (height, weight, BMI, BP, heart rate), medical, lifestyle and family history, and vaccination status. This data helps generate their AI-CVD and pre-diabetes risk scores and predicts mild, moderate, and severe risk. Physicians logging into the app can view the guest's recommendation based on the grading. As of August 2022, the app has captured data for approximately a thousand participants from Delhi and the national capital region. In future directions for this app, we plan to navigate corporate and association-based camps throughout India. Those ProHealth guests who are not up to date or enthusiastic regarding digital formats can access their registration details, medical summary, and reports in paper-based format; physicians can document follow-up test reviews and consultation notes in this file.

**Summary and Conclusions:** A continuum of health and wellness is an integral determinant of QOL and life expectancy. Physical health boosts mental wellness and vice versa, and this synergy underlies the ongoing aptitude for maintaining other important facets of life such as personal and professional goals and socioeconomics. Various factors contribute to the evolution of our health status, including our age, gender, medical history, lifestyle choices, family history, psychosocial factors, and history of injury, trauma, or disability. The rise in NCD-induced premature multi-morbidity and mortality, especially in middle and low-income countries, necessitates personalized screening and early detection to mitigate the risk of onset and progression, drive timely intervention and lower the pharmaco-economic burden. Along with customized

treatment protocols, risk prediction based on scoring tools is also gaining momentum in bolstering overall NCD management strategies. We can combine personalized health screening with individualized risk prediction to guide the evaluation of disease onset and severity, targeted intervention, response to treatment, and monitor and maintain progress with a structured continuum of care. The Apollo Hospitals ProHealth program (designed based on data analyses from approximately 25 million health checks) integrates personalized preventive health screening and AI-powered chronic disease risk scoring to formulate individualized recommendations and care continuum health mentorship. By leveraging technology, the program provides an impetus to the individual to be proactive about their health and wellness, knowing they have a committed care team supporting them on their journey.

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## Case Report

# A Unique Case of Immune Thrombocytopenic Purpura Secondary to Trimethoprim-Sulfamethoxazole Use

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**Highlights:**

- Immune thrombocytopenic purpura is an autoimmune disease characterized by thrombocytopenia and a generalized purpuric rash secondary to exposure to both environmental factors, infections, drugs, foods, or vaccination.
- These triggers cause autoantibodies that lead to platelet destruction and isolated thrombocytopenia (platelets < 100,000/mcL).
- Here, we present a unique case of an individual with a relapse of immune thrombocytopenic purpura secondary to Trimethoprim-Sulfamethoxazole, resulting in a platelet count of 0/mcL.

**Key Words:** Thrombocytopenia, Drug-induced, Petechiae, Purpuric rash, Intravenous immunoglobulin, Steroids

**Introduction:** Immune thrombocytopenic purpura (ITP), previously known as idiopathic thrombocytopenic purpura, is characterized by thrombocytopenia (platelet <100,000/mcL) with normal hemoglobin, normal white blood cell count, and a purpuric rash (1). ITP is characterized by anti-platelet immunoglobulin G (IgG) antibodies, which bind to platelets and lead to phagocytic breakdown (2). The causes of ITP include environmental factors, infections, genetic factors (3), and drugs (4). Trimethoprim-Sulfamethoxazole (TMP-SMX) is an anti-bacterial drug that has commonly been associated with ITP. The drug-dependent antibodies associated with TMP-SMX have been shown to be reactive to both sulfamethoxazole and trimethoprim indicating both parts of the compound trigger thrombocytopenia (5). Initial diagnosis of ITP has been associated with an approximate 40% risk for relapse (6). Patients should be educated on signs and symptoms of ITP to prevent treatment delay as there are numerous agents that can cause thrombocytopenia. Here, we present a patient who

presented with a relapse of his ITP secondary to TMP-SMX.

**Case Presentation:** Signed informed consent was obtained from the patient to publish the case report and photographs. Institutional Review Committee (IRC) case report study exemption was obtained from the Institutional Review Committee (IRC) of Huntsville Hospital, Huntsville, Alabama, USA.

A 58-year-old male with past medical history of sleep apnea, left knee amputation, chronic pain, neuropathy, previous COVID-19 vaccine, and immune thrombocytopenic purpura (ITP) presented to the emergency department with bruising on his extremities (Figure 1) and the back (Figure 2). The patient reported that he had ITP after his left knee amputation requiring hospitalization in a different state in 2018. The trigger for thrombocytopenia in 2018 was not known. He was treated with no complications and has not had any recurrences since then requiring further follow-up visits with hematology.



**Figure 1:** Bruising on the extremities upon presentation to the ER.



**Figure 3.** Bruising on the oral mucosa upon initial presentation to the ER.



**Figure 2:** Bruising on the back upon initial presentation to the ER.

In November of 2021, the patient had undergone a pain pump repositioning surgery to remove a spinal stimulator, and he was given a prescription for TMP-SMX. He reported no symptoms or complications from the surgery. The morning after completing the TMP-SMX prescription, he awoke with bruising all over his body, including his stump, tongue, and oral mucosa (Figure 3).

The patient visited the emergency department where a platelet count was ordered. Zero platelets per mL on admission was found, and this was confirmed on repeat platelet count. Hematology was consulted and the patient was diagnosed with acute immune thrombocytopenic purpura. He was immediately given 125 mg of intravenous (IV) methylprednisolone and continued to receive 80 mg of IV methylprednisolone daily. The patient also received a transfusion of 1 unit of platelets.

The patient was admitted to the hospitalized service and given intravenous immunoglobulin (IVIG) and dexamethasone. He also received 2 units of platelets. The patient's clinical condition improved, and his platelet count rose to 67 platelets per mL, in comparison to zero platelets per mL on admission. His purpuric patches also continued to improve. His hospital course also involved

renal insufficiency, chronic pain, and sleep apnea. His renal insufficiency was managed with IV fluid resuscitation and there were no further issues. His chronic pain was managed with a buprenorphine patch and the sleep apnea was managed with continuous positive airway pressure (CPAP), as he had been using at home. He also experienced mild urticaria secondary to intravenous immunoglobulins (IVIG), but this was managed with cetirizine hydrochloride and diphenhydramine as needed. He was discharged with instructions to follow up with hematology and receive one more day of dexamethasone.

**Discussion:** Immune thrombocytopenic purpura (ITP), or idiopathic thrombocytopenic purpura, is an autoimmune disease characterized by a purpuric rash and thrombocytopenia, with platelets less than 100,000 mL, normal hemoglobin and normal white blood cell counts (1). Some medical centers also obtain serological assays to check for presence drug-dependent antibodies, however this may not always be available (7). Predicting triggers can be difficult as there are many agents that can trigger thrombocytopenia, including drugs, foods (5), disease processes such as severe acute respiratory coronavirus-2 (SARS-CoV-2) (8), or vaccinations (9). These agents result in the development of IgG antibodies that target platelet membranes for destruction (10). After diagnosis, treatment of ITP involves platelet transfusion, and/or glucocorticoids, rituximab, thrombopoietin-like agents, or IVIG. Thrombopoietin nonpeptide agonist like Eltrombopag are reserved for persistent or chronic ITP patients who have had insufficient response to corticosteroids or IVIG. If patients have not achieved remission with pharmacological interventions, splenectomy may also be performed (10).

In this case, we described a 58-year-old male who presented with a relapse of immune thrombocytopenic purpura (ITP). In checking for recent history of drugs or foods that could have triggered the thrombocytopenia, TMP-SMX was noted to be recently prescribed. The thrombocytopenia, in this case, was so severe, the patient's platelet count was noted to be 0. We hypothesize that this patient had IgG autoantibodies to TMP-SMX, and use of TMP-SMX caused an immune response leading to complete platelet destruction (11). Previous studies have described immune thrombocytopenic purpura secondary to TMP-SMX (12-14). Since these autoantibodies can remain in the bloodstream for many years, so the patient should be advised to avoid TMP-SMX in the future (15). The patient was successfully managed using dexamethasone and IVIG and discharged to home in stable condition with instructions to follow up with a hematologist in the future. Use of rituximab in treatment and prevention of future relapses is controversial, given that its effects diminish over

time. Sun et al compared relapse rates in patients who were initially treated with rituximab in comparison with placebo (16). That study also found that after approximately 2.6 years, the protective factor associated with rituximab was insignificant (16). Because this patient had initially been diagnosed with ITP in 2018, the patient was outside of the window for protection from rituximab. Factors that may predict relapse include blood type, being non-O, patient who is younger than 25 years old, or patient who received rituximab. Some studies have suggested that ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) deficiency has been linked to increased risk for ITP relapse, but there were many limitations to these studies that warrant further investigation, therefore we did not test this patient for ADAMTS13 (16). Other studies have associated mean platelet volume (MPV) with an increased risk of ITP (6).

Future research should aim to navigate protective and prognostic factors for ITP given that there are numerous agents that can trigger relapse. It is also hard to predict which offending agent can trigger relapse and which may not. Current literature is showing that the COVID-19 vaccine can trigger ITP. While the patient in this case had been previously vaccinated for COVID-19, this was > 6 months prior to presentation, suggesting that COVID-19 vaccination was not the likely etiology. Understanding predictive factors can allow for patients with a history of ITP to safe timely administration of the COVID-19 vaccine without relapse.

**Conclusion:** This case presents a unique case of relapse of immune thrombocytopenic purpura secondary to TMP-SMX use with a platelet count of 0/mL. Similar case studies have not described a platelet count as low as 0/mL. In acute cases of ITP secondary to TMP-SMX use, it is not advisable to transfuse platelets unless a patient is actively bleeding. Instead, patients should be managed with IVIG and steroids to reduce autoantibody counts in the bloodstream. However, in this case, platelets were transfused as the platelet count was 0. Future research should aim to investigate the role of rituximab or other agents that can protect against ITP relapse.

**Disclosure:** Authors declare no competing interests.

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## Review Article

# Mental Health in Rural Children and Adolescents During Post-COVID-19 Period

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**Abstract:** The COVID-19 pandemic in America is slowly improving but there is a long and uncertain recovery from the psychiatric impacts of COVID-19 for the world, potentially more so for children and adolescents. Youth in rural communities are at heightened risk of suffering worse outcomes from the pandemic as they face numerous physical, technological, economic, and geographical disparities compared to urban and suburban populations. Within these limitations, adolescents remain the most overlooked victims of the pandemic stress placed on rural communities. The forced isolation of the COVID-19 pandemic has translated into a life of reduced social connection, increased time in stressed homes with higher rates of abuse, reduced impact and respite found within schools, and new onset of worsening mental illness and early onset substance use. With these stressors presenting with suicide as its most fatal and growing outcome, proper interventions aimed at improving service to children and adolescents, especially those from rural areas, is crucial at this point in a society's recovery from COVID-19 and careful social re-integration. As communities now begin to recover from many types of losses brought on by COVID-19, steps must be taken to minimize the lasting effects on child and adolescent mental health; by ensuring access to tele-mental health services, preparing schools for the transition from virtual to in-person education by filling academic gaps for those who struggled during the pandemic, increasing follow-up and parent involvement in therapy, strengthening community-based support systems, and ensuring a smooth transition to normalcy, we can bolster our rural communities and improve the mental health outcomes for some of our most vulnerable citizens.

**Keywords:** Child and adolescent psychiatry, Rural medicine, COVID-19, Mental health impact

**The Mental Health Impact of COVID-19:** The COVID-19 pandemic has greatly shaken the world and created lasting stress and trauma to society. From job loss and isolation to illness and death, the impacts of this ongoing pandemic are far reaching, leaving no one unscathed (1). The morbidity and mortality of this virus strike fear and anxiety into the hearts of the populace, as the still growing death count has surpassed 600,000 Americans (2) and 3.9 million people worldwide (3). This statistic is especially troubling for individuals with somatic and psychiatric co-morbidities, which put them at higher risk for more severe disease and complications. Government leaders and administrators have attempted to “flatten the curve”, reduce transmission, and promote social distancing, to varying effects. The goal of the quarantines, used by many nations, was to reduce the risk of COVID-19 transmission and thereby diminish the risk of severe life-threatening respiratory illnesses and deaths; but these “stay-at-home” orders and the subsequent social and emotional isolation inadvertently created long-term psychological and economic sequelae (4-8).

**The Long-Term Sequelae of Pandemics:** As societies work to understand the breadth and depth of the psychosocio-cultural impact of COVID-19, many scholars turn to the lessons of the Spanish flu of 1918-1919 which left 500 million infected and 50 million dead. The historical demographer Sverre Erik Mamelund, reviewed asylum hospitalizations in Norway from 1872 to 1929, finding that the number of first-time hospitalized patients with mental disorders attributed to influenza had increased by an average annual factor of 7.2 in the 6 years following the pandemic (9). Spanish flu survivors reported sleep disturbances, depression, mental distraction, dizziness, and difficulties coping at work. Mamelund also noted an increase in suicides (9). In the decades following, research in Great Britain revealed a rise in nervous symptoms and illnesses among some patients recovering from influenza infection, particularly depression, neuropathy, neurasthenia, meningitis, degenerative changes in nerve cells, and vision changes (9). Current studies and clinical experience indicate that the world is repeating its emotional experience with the Great Influenza pandemic over 100 years later.

**Rural Mental Healthcare Outcomes:** Much of our understanding of worsening social determinants of mental health and their outcomes after COVID-19 come from studies of urban areas. Urban areas have more people, 85% of the US populace, but rural America has more land with 63% percent of U.S. counties classifying as rural (10). Due

to demographic, sociological, economical, and infrastructural differences, the findings for urban populations cannot be extrapolated to rural populations. Because of data collection barriers partially attributed to remote locations with limited funding and infrastructure capacity (11), rural areas have been overlooked when evaluating the impact of COVID-19 on communities, scholars, and healthcare providers. Even before the COVID-19 pandemic, rural communities had disproportionately higher rates of heart disease, cancer, and stroke (10). These conditions increase the risk of morbidity with COVID-19 infections and therefore force more extensive restrictions in these already isolated rural regions. The COVID-19 pandemic has further minimized the potential for social support, particularly for the elderly or individuals with immunosuppressive conditions, who require such isolation to reduce their risk of infection. Rural regions were unprepared for managing the potentially more severe pandemic outcomes as 98 rural hospitals had closed between 2010 and 2019 (10). This is at the same time as rural residents experience less access to medical care and mental health providers (10) and are at increased risk of suffering severe physical and mental health outcomes during this pandemic.

In a swathe of America already experiencing more substance abuse and mental health issues, including 1.5 times the suicide risk of urban counties (10, 11). Suicide risk factors only increased during the pandemic through larger firearm purchases (14), economic and housing instability, increased intimate partner violence, and more prevalent child abuse (15).

**Impact of COVID-19 on Mental Health in Rural America:** The poor mental health outcomes in rural America can be at least partially linked to their poorer prevention practices. A report (16) found that rural Americans were less likely to have used disinfectant, worn a mask in public, worked from home, or avoided public dining compared to Americans in other settings. While suicides overall decreased throughout the United States (18), opioid overdose deaths skyrocketed; from September 2019 through September 2020, there were 87,000 deaths due to drug overdoses (19). While this increasing rate of drug overdoses preceded COVID-19, the biggest leaps in overdose related deaths were seen in the months of April and May 2020, at the height of the pandemic (19). Due to the restrictions placed to prevent the spread of the virus, many substance abuse services were limited, which could explain the large jump in

overdose deaths (19).

Treatment for the individuals at greater risk of suicide and overdose was limited by their location. Rural counties have fewer psychiatrists and psychologists than urban counties, with over 50% of rural counties consistently lacking adequate access to a psychiatrist or psychologist (19). This dearth was temporarily ameliorated with the telehealth waivers during the COVID-19 pandemic, allowing doctors to see patients and prescribe across state lines (10). However, the disadvantages of telehealth require access to a smartphone or computer, broadband internet, and technological skills, which may lack in many vulnerable communities (10). The Federal Communications Commission (FCC) estimates 21.3 million Americans do not have access to broadband but there are also estimates this number may be as high as 42 million (10). This technological disparity worsens the cycle of poverty and mental illness in rural populations by limiting the capacity for remote work, access to telehealth care, and even the use of grocery delivery apps (10). Beyond the predisposing risks existing for rural populations during the COVID-19 pandemic, the lack of technological access further isolates these communities by inhibiting residents from taking advantage of educational, economic, and treatment opportunities that countries relied upon to overcome the unique challenges of the COVID-19 pandemic.

**Impact of COVID-19 on Child and Adolescent Mental Health:** While much of the focus has been on adults, adolescents also faced numerous daily challenges in the COVID-19 pandemic. School lockdowns lead to virtual learning and physical distancing from community activities, peers, and friends (20). While no formal studies have been done on rural children and adolescents in the United States, lessons can be taken from the few studies of international rural youth. One Chinese study on rural high school students during the outbreak found a high prevalence of mental illness symptoms, including anxiety, depression, and PTSD and a sizable amount of suicidal behavior, including attempts (21). With schools virtual, students may have felt added pressure to perform as well academically as they did before the closures, but without the same support they had with in-person schooling. The lost connection with friends and peers due to restrictions and general fear of contracting the virus could have contributed to the poor mental health findings (22).

Another Chinese study of children and adolescents

during the COVID-19 pandemic found that over 20% of respondents had clinical depressive symptoms (22.28%) and there was a significant positive correlation between respondent's anxiety level about the virus and their depressive state (23). The study also found that, compared to pre-pandemic period, children and adolescent anxiety levels were much higher during the pandemic, specifically social phobia in adolescents (23). A study in India found that over 60% of the surveyed subjects had experienced depression, anxiety, and/or stress after two months of quarantine (24). An interesting finding to note was that living in urban areas, rather than rural, was protective against any psychological impacts from the pandemic, possibly due to increased resources and social connectedness (24).

Children who come from disadvantaged backgrounds, such as low income, domestic instability, or chronic illness, face the highest risk of suffering the worst long-term outcomes from the pandemic (25). The consequences of the stressors can be devastating, stunting their education, and limiting their social development. With fewer support systems in place due to pandemic-related restrictions, these already disadvantaged children are left with limited options to meet their medical and psychological needs.

#### **Adolescent Suicide Rates During COVID-19:**

Adolescent suicide rates have been steadily increasing (26) and with worsening mental health conditions due to the pandemic, one can assume the suicide rate will continue to rise. The transition back to normalcy will be difficult for many, as returning from a prolonged social isolation can bring on feelings of social anxiety, especially in those with pre-existing mental illness. The pandemic created an excuse for children and adolescents with social anxiety to minimize their contact with others, feeding into their anxiety and allowing them to avoid therapeutic exposures.

#### **Substance Use Among Adolescents During COVID-19:**

The impact of the pandemic on adolescent substance use has a more complicated trajectory. In a study by Dumas et al. conducted three weeks post-COVID social distancing orders, results showed a 1/5 to 2/5 in the percent who binge drank, used cannabis or vaped, in a sample of 14 to 18- year-old adolescents. The study further showed no change in alcohol use in this population (27). Interestingly, the pandemic seemingly strengthened protective factors known to mitigate substance use in adolescence. A national survey has

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shown that adolescents with risk factors for substance use benefit from increased time spent with family as parents have the largest influence over their children's decisions and actions regarding substance use (28). The pandemic has also enforced social distancing, alleviating social pressures to engage in substances by mitigating exposure to peers who use substances and anxieties related to social enhancement in the school setting (29). Unfortunately, Dumas' study reveals these protective factors only apply to some populations or can transition to risk factors with time. With more time spent in the household, the more exposure to substance use increases if the adolescent lives with a parent or family member with a substance use disorder, a significant risk factor in engaging in substance use themselves. About 1 in 8 children (8.7 million) lived-in households with at least one parent who had a substance use disorder in the past year (30). To promote "social distancing" and curtail the spread of the virus, schools have transitioned to virtual learning, recreational activities were canceled, and efforts were made to prevent social gathering in public areas. This social regression has stunted the adolescent's emotional growth by ingraining social isolation into normal practice. A cross sectional study found a positive correlation between loneliness and depression, anxiety, and drug use in young adults during the COVID-19 pandemic. Data show significantly elevated reports of loneliness compared to before the pandemic along with increased harmful or dependent levels of drinking (30%), with 44% reporting binge drinking at least monthly as a coping mechanism.

While only 22% of Dumas' sample reported using drugs, 38% of those users reported severe drug use (31). Further, anxieties to fulfill a certain social status continued to be prominent in adolescents' daily life and another driving factor in the surge in adolescent substance use despite social distancing measures. Findings indicate that adolescents higher in self-reported popularity were more likely to engage in peer substance use during the COVID-19 pandemic by way of social media or even in-person (27).

**Discussion:** The COVID-19 pandemic in America is slowly improving but there is a long and uncertain recovery from the psychiatric impacts of COVID-19 for the world, potentially more so for children and adolescents. Youth in rural communities are at heightened risk of suffering worse outcomes from the pandemic as they face numerous physical, technological, economic, and geographical disparities compared to suburban and

urban populations. This is difficult to quantify with the limited funding for research on rural areas, with previous studies providing inaccurate data due to large standard deviation values.

Within these limitations, adolescents remain the most overlooked victims of the pandemic stress placed on rural communities. The forced isolation of the COVID-19 pandemic has translated into a life of reduced social connection, increased time in stressed homes with higher rates of abuse, reduced impact and respite found within schools, and new onset of worsening mental illness and early onset substance use. With these stressors presenting with suicide as its most fatal and growing outcome, proper interventions aimed at improving service to children and adolescents, especially those from rural areas, is crucial at in a society's recovery from COVID-19 and careful social re-integration. As communities now begin to recover from the many types of losses brought by COVID-19, steps must be taken to minimize the lasting-effects from the pandemic on child and adolescent mental health and services must be accessible to those struggling to adapt to their new normal.

#### **Recommendations:**

- **Technology:** We recommend ensuring children and adolescents can access and use technology to avail mental health care as telehealth models in many regions may persist beyond the end of quarantine and social isolation. Receiving specialty services to improve technological literacy, applying for grants to improve technological access, and working with local government agencies to improve internet access parity in all regions will address this major barrier to mental healthcare.

- **Schooling:** Virtual schooling presented many issues for families, as caregivers were assigned additional responsibility of watching over their children during virtual schooling. Additionally, not all families had the necessary resources to provide a conducive learning environment at home. Distractions such as siblings, domestic issues, or shared spaces, lead to reduced participation from the child in virtual schools and may have interfered with their ability to learn. This last point is especially important in vulnerable children, including those who are inattentive and easily distracted, as these individuals require structure and authority figures to redirect their focus. As schools increasingly return to in-person learning, academic infrastructure must prepare for children struggling with acclimating to larger groups of people as well as requiring

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1:1 service to assist with filling academic gaps formed for those who struggled with virtual education. We recommend working with local school systems to review the success and failures of virtual schooling and address the shortcomings to ensure vulnerable students do not fall through the cracks and become left behind in their academics.

• **Increasing Follow Up and Parent Involvement in Therapy:** Children and adolescents have incurred serious changes to their routines since the start of the pandemic. With changes in schooling and cancelled activities, children were left with reduced social contact and suffered from feelings of loneliness and isolation. To minimize the possible impacts on their well-being and mental health, children and adolescents should have more frequent follow-up sessions with therapists to ensure they are adapting well and handling the extra pandemic-related stressors they now face. By frequently checking-in with their patients, therapists are more likely to catch and/or prevent potential self-defeating behaviors and reduce the risk of decompensation.

During virtual therapy sessions, caregivers should be encouraged to sit-in on the sessions to ensure the child participates in distance-based therapy. With individuals who are easily distracted or with severe mental illness and disability, virtual therapy reduces the therapist's ability to connect with their patient and can lead to decompensation. Caregivers can ensure that the child is participating with the therapy and can also assist with notetaking and providing feedback. During such a difficult time, extra involvement by the caregiver with therapy can ensure the child or adolescent can not only maintain progress but also improve in the context of the pandemic.

• **Community-Based Initiatives:** To undo the new onset anxiety that comes from reacclimating to larger communities, we recommend families engage relatives outside the home, neighbors, or family friends to help reintroduce socialization amongst children and adolescents. While in person school will serve as a major exposure, some children with existing psychiatric illnesses may struggle to adjust to the increased stimulation and will benefit from gradual increase in socialization. This gradual re-establishment of a sense of community will help individuals overcome feelings of loneliness and provide a safe outlet to engage with friends.

• **The Overall Transition to Normalcy:** We recommend approaching all children, but particularly those with lower access to social care resources and geographical isolation, by addressing the growth and losses each child has experienced in academics, emotional expression, family unity, friendships, connection with the world they have known and at large, and sense of personal well-being. By learning to recognize their own resilience in adapting during a life-altering pandemic, patients can evaluate their failures with a perspective rooted in determination and self-belief to overcome their challenges.

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**This Section Contains Non-Peer Reviewed  
Synopsis of CME Lectures and Abstracts  
of Research Posters Presented at the  
40<sup>th</sup> Annual Convention and Scientific  
Exposition of AAPI, Atlanta, GA, June 2022**



## Synopsis of CME Lecture – 40<sup>th</sup> Annual AAPI Convention 2022

### Recent Advances in Resuscitation – 2022 Updates Targeted Temperature Management

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**Cardiac Arrests and Resuscitation Guidelines:** Cardiac Arrest remains the leading cause of morbidity and mortality globally. AHA's 2020 Resuscitation guidelines added a new "Recovery Link" for the "Chain of Survival" and a new scheme for "neuro-prognostication" was given to guide critical decisions of management (1). About 12-19% of COVID-19 patients may need hospitalization and 3-6% may be critically ill due to ARDS, myocardia injury, malignant arrhythmias and shock. There was a 119% increase in out-of-hospital cardiac arrests (OHCA) during the pandemic compared with earlier control periods in a meta-analysis from 10 countries. Mortality was 85% compared with 62% for the control periods. A recent study from Western Australia (with a low incidence of COVID-19), OHCA incidence and survival were similar to pre-COVID 19 periods.

Rescuer attitudes and delays towards resuscitation were influenced by the fear of contracting COVID-19. The American Heart Association (AHA) 2021 Interim Guidance during COVID 19 outlines the precautions during resuscitation of patients in cardiac arrest including in special situations such as pregnancy and opioid-overdose. "Perimortem cesarian delivery" within five minutes after the cardiac arrest was highlighted (2).

**Cardiac Arrest Registry to Enhance Survival (CARES):**

"Warangal Area Cardiac Arrest Registry" WACAR" (Dr. Vemuri Murthy is the Co-Investigator) is the first OHCA Registry from India based on a "Modified Utstein Template" (3). This is a prospective one-year observational cohort study of OHCA in Warangal, Telangana, India, with 814 subjects of OHCA brought to a tertiary care hospital. The study identified cardiac etiology as the most common cause of OHCA with a preponderance in males with a median age of 60. Majority of OHCA's occurred in residential locations and during daytime. Hypertension, diabetes, and tobacco use were the common risk factors

noted. There were no survivors in the study. Currently WACAR is conducting the second observational study during COVID-19 pandemic.

**Cerebral Protection and Updates on Targeted Temperature Management:**

Brain is highly susceptible to oxidative stress due to multiple factors involving glucose, calcium, lipid peroxidation, neurotransmitter auto-oxidation, redox signaling, mitochondrial dysfunction etc. Several unsuccessful trials were conducted to identify a neuro-protective agent utilizing various agents such as statins, barbiturates, glutamate blockers, melatonin, beta blockers, corticosteroids, growth factors, free radical scavengers (Mannitol), immunosuppressants etc. There is some recent research indicating neuronal regeneration with new synaptic connections. The destructive processes following ischemia and reperfusion result in the production of free radicals, increases in cell membrane leakage, DNA injury, apoptosis, increased cerebral metabolism, coagulation cascade activation etc. There is evidence that these destructive processes can be reversed or mitigated by "Therapeutic Hypothermia", currently called "Targeted Temperature Management" (TTM). *Besides TTM, no other neuroprotective interventions have been identified yet in translational medicine involved with neuroprotection.* One of the earliest Randomized Control Trials (RCTs), "Hypothermia after Cardiac Arrest Study" was done in 2002 in a population of 275 Out-of-Hospital Cardiac Arrests (OHCA) due to a shockable rhythm comparing subjects with a TTM 33 °C versus normothermia (37 °C). The primary outcome was a favorable neurological outcome at 90 days with significant lower mortality in the hypothermia group. Similar results were obtained in another RCT in 2002 in a population of 77 (4). However, a 2013 RCT involving 939 subjects managed with a TTM 33° C Vs 37° C, no significant differences were found between the two groups in outcomes (5). Similar results

with no significant outcomes with hypothermia were noticed in two other RCTS (6 & 7). The 2019 HYPERION trial RCT (8) with 581 subjects in OHCA and IHCA (In-Hospital Cardiac Arrests) with non-shockable rhythms with TTM at 33 °C versus normothermia 37.5 °C showed significant improvement in neurological outcomes of hypothermia group versus normothermia group at 90 days. The most recent RCT by TTM 2 trial) in 2021 involving 1861 OHCA subjects with a presumed cardiac cause was conducted with a TTM at 33°C vs targeted hypothermia 37.5°C. No significant differences between the groups were noticed (9).

TTM 2 was a critical study because it highlighted and brought to the forefront the question of “Are we doing hypothermia correctly?” The delay in hypothermia is essentially preventing the beneficial effects of cooling to truly take effect, so we are comparing an ineffective therapeutic arm to a control arm, and hence no difference is seen.

**The Current Consensus:** *TTM is a Class 1 AHA Guideline in resuscitated comatose patients. There are not enough evidence-based studies yet to support the advantage of 36°C compared to 32-33°C for cooling temperatures and other issues.*

**The most recent (2022) recommendation of the European Resuscitation Council is:** “There is currently insufficient evidence to recommend for or against temperature control at 32-36°C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this. We recommend not actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia”.

**The unresolved questions are:**

- Is it hypothermia or prevention of fever that favors neurological outcomes?
- Is fever harmful for post-resuscitation outcomes? Is temperature control beneficial, or is it the protocolized care and delayed prognostication that matter?
- Could hypothermia be beneficial if we could reach hypothermic temperatures faster?
- Does optimal temperature management depend on etiology, rhythm, or other patient characteristics?

**ICECAP Trials:** Currently in the USA, some Institutions are conducting National Heart, Lung, and Blood Institute (NHLBI) funded clinical trials studying the influence of “cooling duration” on the efficacy in cardiac arrest patients. The hypothesis is: longer durations of cooling may improve

either the proportion of patients that attain a good neurological recovery or may result in better recovery among the proportion already categorized as having good outcome.

The randomized adaptive clinical trials will have several possible treatment arms with varying cooling durations to characterize the duration-response curves and determining the optimal duration of cooling in survivors of OHCA. Both the shockable and non-shockable cohorts will be also studied as distinct populations.

In conclusion, currently there are many gaps in the knowledge of the TTM that need to be bridged. The future direction of TTM depends on more powered RCTs answering the basic questions.

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**Acknowledgement:** Contribution of the following experts to the presentation is kindly acknowledged.

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## Synopsis of CME Lecture – 40<sup>th</sup> Annual AAPI Convention 2022

# Physician Contracts and Non-Competes in Texas: What You Really Need to Know

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Whether a Texas physician<sup>1</sup> has been presented with a contract, or, as an employer, is hiring another physician, here are the concepts that really matter:

**Concept No. 1: Determination of Duties, Practice Location, and Work Schedule:** A health care (HC) contract should clearly confirm that the employee will observe and comply with such rules, regulations, and policies as the employer may institute occasionally. Fundamentally, the contract must establish where the employee will perform duties, and what those duties are. The employer will want some discretion and flexibility in assigning the employee to various locations if needed. The employee will want to limit the employer's unilateral ability to assign new locations so as to not have to travel far on a regular basis and to protect against possibly enlarging the radius of any post-employment non-compete. The best solution may be to allow the employee an ability to consent to any change or additional location. As for duties, the contract will likely have a fairly broad description, which allows for flexibility when it comes to the performance of actual employment duties on a practical basis.

**Concept No. 2: Payment of Salary and Bonus:** Compensation and how such compensation may change throughout the term of the employment contract should be clearly set forth in the document itself or in an exhibit. Unless salaried, it is crucial that the compensation calculation algorithm be as clear as absolutely possible. Setting forth specific examples of levels of production and showing how certain bonus calculations result can greatly help clarify. Moreover, physicians are subject to various regulatory restrictions (such as state and federal anti-kickback laws), and so must comply with such regulations,

such that they fall into any necessary employment "safe harbors," which also would require that that any compensation not exceed "fair market value" as well as be "commercially reasonable."

**Concept No. 3: Confidential Information and Trade Secrets:** An HC contract must contain protections for the employer's confidential information and trade secrets, as such confidential information. Although HIPAA protections obviously must also be in place, and the employee must receive adequate and regular HIPAA training from the employer, the HC contract must further set forth a clear and specific definition of what constitutes confidential information. The HC contract must also require that the employee only use such confidential information in the course and scope of the employee's duties and solely to benefit the employer. The HC contract should also require that the employee surrender any and all such confidential information at termination. Segregating employment information (especially confidential information) from the employee's personal information at the start of and during the employment relationship makes the surrender process at termination much simpler and less likely to cause disputes.

**Concept No. 4: Use of Name and Likeness and Intellectual Property Rights:** What rights will the employer and employee have, respectively, to the employee's name, likeness, and intellectual property (IP) developed during employment? Many HC contracts contain provisions that allow the employer to use the name and likeness (e.g., photographic and/or digital images) on the employer's website and in the employer's marketing efforts. The HC contract may also dictate that all intellectual property rights (e.g., patents, formulae, ideas,

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<sup>1</sup>For states other than Texas, please consult the specific law of each state.

inventions, processes, copyrights, know-how, proprietary information, trademarks, trade names, or other developments for future improvements) that are conceived through the employee's work while he/she is an employee are the property of the employer, and that all royalties, fees, or other income attributable to such intellectual property will be the property of the employer. There may be an exception for any intellectual property developed through the employee's sole effort (i.e., without collaboration, assistance, or resources from employer, and while outside the scope of employment).

**Concept No. 5: Malpractice Coverage and Tail:** What about the payment of professional liability (malpractice) insurance (PLI) and who pays for the malpractice "tail coverage" when employment terminates. In the HC contract, the employer typically agrees to provide PLI coverage covering the employee and the employer regarding the services from such insurers as the employer may determine is necessary. "Occurrence based" PLI is triggered on the date of the patient care event and is generally more expensive to maintain. "Claims made" PLI is triggered on the date the claim is made and is generally less expensive to maintain. If PLI coverage is provided on a "claims made" basis, there becomes a need for extended reporting coverage when the HC contract terminates, which is called "tail coverage." Although sometimes negotiable, an HC contract can require that "tail coverage" shall be obtained and the premium paid by the employee, with the employee providing evidence of such tail coverage furnished to the employer in a certain amount of time after termination.

**Concept No. 6: Notice of Termination and Grounds:** The timing and grounds for employment termination must be agreed upon, understood, and clearly set forth by the HC contract. It is important for the employee to understand the reasons that employment can be terminated for cause, whether there is any heightened requirement for such termination (like a 2/3rds vote of partners), and whether there is any cure period to rectify the alleged breach. Certain events will almost always result in a for cause termination (loss or restriction of professional or DEA license, loss or restriction of medical staff privileges, loss, or failure to renew board certification status, felony

conviction, etc.). However, the HC contract may also contain some "looser" and arguably more subjective reasons for termination, such as failure to faithfully and diligently perform the duties required under the HC contract and/or to comply with the reasonable policies, standards, and regulations of the employer. The employee must realize that as specific as the grounds may be, the employer will have wide discretion in its decision to terminate for cause.

**Concept No. 7: Non-Compete Restrictions:** An employment-based non-compete is a restrictive covenant that prohibits a former employee from competing with a former employer within a specific geographic area for a specified period after the end of the employment. Courts had long viewed these with disfavor as "restraints of trade." But various statutes and case law decisions in Texas now make it clear that, as long as the non-compete protects the employer's legitimate business interests, courts will generally uphold them as long as they are not overly restrictive to the employee's ability to make a living and not against public policy.

For a non-compete to be enforced against a physician's practice of medicine in Texas, certain statutory requirements must be met, including an option for the physician to "buy out" the non-compete at a reasonable price, or as determined by a mutually agreed-upon arbitrator.<sup>2</sup> Other requirements include that the non-compete restriction not deny the physician access to a list of his patients whom he or she has seen or treated within one year of termination of employment, that the employer provide certain access to medical records for a reasonable fee, and that the physician will not be prohibited from providing continuing care and treatment to patients during an acute illness even after the employment has been terminated. Finally, for all employees (physician and non-physician), the non-compete restriction must have sufficient "consideration," so it is not just an "illusory" promise. Texas case law holds that basic training and confidential materials given to employees at the beginning of the employment relationship sufficiently establish this consideration.<sup>3</sup>

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<sup>2</sup> See § 15.50(b) of the Texas Business Code.

<sup>3</sup> Again, for states other than Texas, please consult the specific law of each state.

**Concept No. 8: Non-Solicitation Restrictions:** A non-solicitation restriction, if it relates to patients, can have as much if not more impact on an employee as a non-compete restriction. Such a provision is not a *per se* prohibition from practicing the profession but may purport to restrict the solicitation of patients and sources of future patient referrals outside the non-compete radius. As with any non-compete language, and depending on an employee's leverage, he/she could eliminate or severely narrow such provisions, as well as ensuring that such provisions only prohibit the solicitation of current patients, referral sources, and employees rather than potential ones, and clarify that any such restrictions do not apply to after-acquired locations.

**Concept No. 9: Avoiding Patient Abandonment:** No matter how the HC contract terminates, all precautions must be taken to ensure continuity of care for patients. Technically, to avoid any claim of patient abandonment, a Texas physician ending the physician/patient relationship should give thirty-days' notice of the patient's current status, the patient's present and future needs, explanation of the consequences of non-treatment, recommendation that the patient continue care with another physician, and a clear statement that the physician remains available to provide any necessary emergency treatment during the

thirty-day period. If a physician is departing the employer, the required notice to patients under Texas Medical Board Rule 165.5 will likely suffice.

**Concept No. 10: Strive for Fundamental Fairness:** The foundation of the employer and the employee relationship is trust, which means the HC contract should be fundamentally fair. If the employment relationship is to prosper over the long term, both employers and employees need to be treated equitably. However, employers will almost always set the parameters of the employment relationship, including the initial drafting of the HC contract offered to the prospective employee. But an HC contract that overreaches may result in the potential employee choosing another employer or might otherwise jeopardize the employee's trust in the employment relationship. So, it is best to be fair.

**Disclosure:** Author focuses on the representation of Texas physicians and physicians in training. She helps physicians maintain their professional records while seeking practical pathways to the resolution of their business, legal, and ethical issues that arise in their medical practice.

**Disclaimer:** This material is provided for informational purposes only and is not intended to be legal advice.

## Synopsis of CME Lecture – 40<sup>th</sup> Annual AAPI Convention 2022

# Telemedicine: Novel Practices and Policy Changes and Reimbursement Solutions

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### Highlights:

- Telemedicine is defined, as are recent policy changes enabling telemedicine's growth, which was accelerated by the COVID-19 public health emergency.
- The AMA has engaged in the informed expansion of telemedicine through advocacy and partnerships and studies centered on telemedicine value, experience, and implementation.
- Artificial intelligence (AI) will continue to expand and affect digital medicine. A recent taxonomy to describe the role of AI in clinical care and/or procedures is discussed.

**Introduction:** Telemedicine expanded rapidly in the early months of the COVID-19 public health emergency. This expansion was due to a rapid convergence of: maturation of technology, consumer demand, and favorable public policy. This circumstance creates challenges and opportunities for physicians considering expanding their telemedicine offerings to patients.

**Background:** Telemedicine is defined as a two-way, real-time audio-visual, interactive communication. Telehealth is a broader term that includes telemedicine but also other modalities, such as teleradiology, remote patient monitoring, and remote therapeutic monitoring (RPM). Audio-only includes the traditional telephone, while store and forward involves stored patient data for review, interpretation, and reporting later.

**COVID-19-Related Policy Change:** Long-standing challenges to telemedicine use include originating-site restrictions, geographic limitations, restrictions on store and forward, limitations on providers, and limits on billing codes covered. Before COVID-19, several advancements had been made. Among the advancements is the greater use of RPM for both acute and chronic disease. Originating-site expansion includes telestroke, evaluation and management sites, Native American Health Service facilities, and dialysis centers.

The public health emergency prompted public policy favorable to telemedicine. Health and Human Services Secretary Alex Azar declared a Public Health Emergency (PHE) on January 31, 2020, and President Trump made a national emergency declaration on March 12, 2020. These two actions triggered the 1135 waivers, named after Section 1135 of the Social Security Act. Such waivers waive or modify Medicare, Medicaid, and CHIP requirements to meet beneficiary needs during the emergency period for affected areas. The 1135 waivers ensure that health care items and services are accessible. These waivers grant far-reaching authority to make modifications, for example, to program participation, pre-approval requirements, and state licensure requirements. In broad terms, the general telemedicine allowances included: (i) all Medicare and Medicaid beneficiaries considered eligible, (ii) coverage, wherever patients and providers are located, and (iii) providers' waiving Medicare co-payments.

The HHS secretary (Xavier Becerra) must renew the PHE every three months for the 1135 waivers to remain in effect. Renewal has occurred 10 times since the original PHE declaration, most recently in July 2022. These renewals are relevant since the 1135 waivers end when the PHE ends. Stakeholders and policymakers must decide which PHE-related policies stay, which go, and which are modified.

**AMA Actions Around Telemedicine:** The AMA has a long history of engagement around digital medicine. In 2019, the AMA convened the AMA Digital Medicine Payment Advisory Group (DMPAG), whose focus included coding/payment for digital health/medicine, artificial intelligence, and advocacy. DMPAG accomplishments include the creation of a taxonomy in coding for digital health, the development of payment pathways for AI and such related services as digital therapeutics, and a focus on geographic and originating-site restrictions. Along the way, the DMPAG fosters the continued dissemination of data on the effectiveness of digital medicine.

**The Value of Telemedicine:** The rapid expansion of telemedicine has enabled sizable data on the value and effectiveness of virtual care. The AMA, in collaboration with multiple organizations and institutions, published the Return on Health: Moving Beyond Dollars and Costs in Realizing the Value of Virtual Care (1). The report presents a framework for measuring the value of digitally enabled care based on several environmental factors: type of practice, payment arrangement, social determinants of health of patient populations; clinical use case; and virtual care modality. These environmental factors were applied to the virtual care value stream: clinical outcomes, quality, and safety; access to care; patient, family, and caregiver experience; and financial and operational impact. Health equity is integrated into each step in the virtual-care value stream.

Several case studies are included in the report, such as an informative one from Virginia Commonwealth University centered on their telepsychiatry efforts during the COVID-19 public health emergency. Positive evidence of program impact includes maintained continuity of care, improved satisfaction with outpatient services and inpatient services, satisfaction with inpatient care virtually, lower no-show rates, and maintained access across various age groups.

Practicing physicians considering expanding their telemedicine offerings may also wonder about the experience of other physicians and their patients. The COVID-19 Telehealth Impact Study, last updated in May 2021 applies claims-data trends and surveys to study the COVID-19-related growth in telehealth. A few highlights from that report are relevant. When asked about which medical problems are being addressed with telehealth, respondents overwhelmingly indicated behavioral and mental health. When asked about future use, greater than two-thirds of physicians and patients indicated agreement to do so.

**Payment for Telemedicine:** Payment for telemedicine services is important in determining viability for a practice. Medicare payment centers on Telehealth Services List categories. Category 1 includes those which are “permanent based on similarity to services already on Telehealth Services list. Category 2 includes services which are “permanent based on demonstrated clinical benefit to the patient. Category 3 is a newly proposed category for temporary addition through the calendar year in which the PHE ends.

Once the determination to move forward with telemedicine expansion is made, implementation becomes key. The AMA published Telehealth Implementation Playbook to help guide decision-making (2). The guide describes activities to be performed in the planning stages, such as evaluating vendors and contracting. During implementation, such activities as

workflow, defining the care team, and evaluating success are included.

**Artificial Intelligence:** When considering digital health expansion, artificial intelligence (AI) often surfaces. Recently, the AMA DMPAG collaborated to create an AI taxonomy for medical services and procedures. The CPT® Editorial Panel accepted the addition of a new Appendix S to describe work associated with AI-enabled services and/or procedures. The service components include: primary objective, which provides independent diagnosis and/or management decision, analyzes data, and requires physician or other qualified health care professional interpretation and report. Based on these components, three categories were created: assistive, augmentative, and autonomous (3).

**Conclusion:** Telemedicine expansion has been rapid, accelerated by the COVID-19 PHE. Studies on the effectiveness and preferences around telemedicine are available to inform practices considering expanding their telemedicine offerings. Overlying this decision-making process is the expansion of artificial intelligence.

**Disclosure:** Author declares no competing interests.

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**AAPI CONVENTION & SCIENTIFIC ASSEMBLY**

AMERICAN ASSOCIATION OF PHYSICIANS OF INDIAN ORIGIN

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## ABSTRACTS OF THE ORAL AND POSTER PRESENTATIONS BY YPS & MSRF MEMBERS

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(2022-23)

ABSTRACTS ARE NOT PEER-REVIEWED

**OR – Oral Presentation; PO – Poster Presentation**

**AAPI-22-001-OR: Evaluation of Plant-Based Consumption and Obesity in the San Antonio Indian Community**

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**Background:** Increased obesity rates have paralleled increased intake of animal products at the expense of plant-based intake. The literature suggests that plant-based intake can improve metabolic health and decrease BMI. However, studies are limited on the impact of plant-based intake among racial minority groups. In 2019, a needs assessment survey was conducted at the IASA Health Fair that identified nutrition as one of the community's top health concerns.

**Objectives :** This study aims to explore the potential relationship between plant-based intake and obesity in the San Antonio Indian Community.

**Methods:** Attendees were surveyed at the IASA's annual community health fair. Participants were self-selected to visit an information booth or engage with volunteers who approached them. Participants independently completed anonymous physical surveys. Correlational analyses and multivariate regressions were performed using Microsoft Excel.

**Results:** There were 115 responses (54% male), and 88% of participants identified as South Asian. In the 40+ age group, intake of non-starchy vegetables and mushrooms was significantly correlated with lower BMI ( $P < .05$ ). After adjusting for age, educational attainment, and other aspects of diet, only increased intake of gourds and mushrooms was significantly correlated with lower BMI ( $P < .05$ ) in the 40+ age group. In the 18-39 age group, there was no significant relationship between plant-based intake and BMI. Vegetarian status, fruit intake, and meat intake were not significantly correlated with BMI in either age group.

**Conclusion:** Plant-based intake, specifically non-starchy vegetables, had a more significant impact on BMI in the 40+ age group compared to the 18-39 age group. Although only two vegetable categories were significant in the multivariate analysis, vegetable intake was moderately correlated between categories, and we conclude that

aggregate non-starchy vegetable intake may relate to lower BMI. The following steps include developing an interventional study based on these findings to understand whether plant-based intake can directly lower BMI.

**AAPI-22-002-OR: Deep Venous Thrombosis. A Retrospective Study in a Tertiary Care Center, South India**

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**Background:** Venous thrombosis is a condition of abnormal thrombus formation in the deep veins. It manifests as Deep venous thrombosis (DVT) and pulmonary embolism, although DVT is the most common manifestation. If not treated promptly, it can cause significant mortality and morbidity.

**Objectives :** The study is undertaken to determine the proportion of unprovoked and provoked DVT, the precipitating factors of provoked DVT, and the types, duration, and complications of treatment along with following up with the patients.

**Methods:** Our study population included 100 patients with radiological evidence of lower limb DVT from January 1, 2019, to December 31, 2019. It is a cross-sectional observational study where clinical data were taken using Electronic Medical Records. Further data regarding compliance and development of complications while on anticoagulation was taken using OAT clinic data of the hospital. The results obtained were analyzed and compared by statistical methods and conclusions drawn.

**Results:** Most DVT belonged to the age group 51- 70 (49%). 54% were women, and 46% were men. The significant risk factor was malignancy. The majority showed no complications of DVT. The majority were treated with warfarin than NOACS. The majority who were treated for <6 months had a good follow-up, while a significant number on indefinite treatment showed poor follow-up. The majority who developed clinically significant bleeding while on treatment were on warfarin.

**Conclusion:** Some of our findings differ from the published reports. While most patients are still being treated with warfarin despite better compliance with NOACS, a rising trend in NOACS usage is seen. An increased risk of

bleeding with warfarin than NOACS needs particular attention, especially when a significant proportion of patients on indefinite treatment were lost to follow-up. A stringent clinical and laboratory monitoring of treatment and patient education is a need of the hour.

### **AAPI-22-003-PO: Is Matching into an Interventional Radiology Residency Competitive? – Evaluation of the 2020 and 2021 NRMP Match Results**

**Rao G, Kroma G, Suri R.** University of Texas Health Sciences, San Antonio, TX, US

**Background:** The National Residency Matching Program (NRMP), which was created in 1952, is a private, non-profit organization focused in providing an efficient means by which preferences of residency program directors are matched with the preferences of eligible applicants for U.S. residency positions. The results of the match are investigated and made available every March in the Main Residency Match Data and Reports section of the NRMP.

**Objectives:** To evaluate outcomes of senior medical students from the 2020 and 2021 ACGME integrated interventional radiology residency match.

**Methods:** Results obtained between the 2020 and 2021 match were assessed to provide guidance for eligible senior medical students. Understanding the competitiveness of a specialty is important to guide medical students on choosing a specialty that would help guide rank lists.

**Results:** The 2021 NRMP match data shows 478 total applicants applying for 162 IR positions compared to 2020 NRMP data showing 444 total applicants applying for 156 IR positions. 2021 ACGME match data demonstrates approximately three applicants applying for every one IR position, which was steady compared to the prior year.

**Conclusion:** Comparing the match data available through the NRMP from 2020 to 2021 suggests that the integrated interventional radiology residency is a very competitive specialty for senior medical students. Evaluation of the 2021 match data would suggest that senior medical students applying in the 2021-2022 match cycle can expect the integrated interventional radiology residency to continue to be a competitive residency in the following ACGME match cycle.

### **AAPI-22-004-PO: Are Leaded Caps Effective at Reducing Radiation Exposure?**

**Rao G, Kroma G, Suri R.** University of Texas Health Sciences, San Antonio, TX, USA.

**Background:** Many advances in understanding radiation exposure have guided the development of effective thyroid shields, leaded aprons, and more recently the use of leaded glasses. The literature on the use of leaded caps has yet to be explored as extensively.

**Objectives :** To provide guidance on what to consider when evaluating a leaded cap.

**Methods:** Explored the literature on the effectiveness of reducing radiation exposure through the use of leaded caps.

**Results:** Leaded caps can be used as an additional tool to mitigate radiation exposure to the interventional radiologist. A review of literature on leaded caps has shown mixed results with a few studies demonstrating that a .5 mm leaded cap to be highly effective at reducing scatter to the brain when compared to only the use of a lead glass shield, while other studies having shown radiation protective caps to have minimal clinical relevance. The brain is one of the more resistant organs to radiation damage and is protected by the skull, which attenuates approximately 40% of scattered radiation. The overall risk of malignant brain tumors is low, which makes it difficult to draw linear conclusion of brain cancer risk and radiation exposure.

**Conclusion:** Innovations in radiation safety are important to understand in order to reduce the risk of ionizing radiation to the interventional radiology physician. The literature is inconclusive at this point on whether the utilization of leaded caps demonstrate significant improvement in radiation safety. However, the literature overall favors minimal to no improvement in radiation safety compared to the standard radiation combination of (leaded vest, thyroid shield and leaded glasses).

### **AAPI-22-005-PO: Social Determinants of Type 2 Diabetes Mellitus Complications in the Hispanic Population of South Texas**

**Lu J, Nguyen T, Patel K, Shah P, Vu A.** UIW School of Osteopathic Medicine, San Antonio, TX, USA.

**Background:** The incidence of Type 2 Diabetes Mellitus (T2DM) is increasing across all ages, including its complications due to social determinants of health.

**Objectives:** To further analyze various social determinants of health and diabetic complications in South Texas.

**Methods:** We hypothesized a higher incidence of diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and amputations in Hispanic populations due to social determinants of health. We reviewed the effects of ethnicity, culture, income, education, and language barriers on diabetic complications within the Hispanic population.

**Results:** The results of our literature review support that disparities in South Texas predispose Hispanic patients to T2DM and its complications.

**Conclusion:** The results from our literature review highlights the need for local and national initiatives to tackle disparities that determine the healthcare outcomes of patients suffering from diabetic complications.

### **AAPI-22-006-PO: An Exceptional Manifestation of Snake Bite**

**Harimohan H, Thomas M.** Department of Internal Medicine, KIMS Health Trivandrum, India.

**Background:** Snake bites have become a major health concern in India. Aplastic anaemia is a rare hematological disorder due to decrease in the bone marrow stem cells.

**Case Description:** A 17-year-old previously healthy boy presented with a history of suspected snake bite on his right big toe. He had features of severe sepsis, DIC and multi-organ dysfunction. He was given several units of blood products, anti-snake venom, antibiotics and supportive care. During the course of the treatment, his sepsis cleared but he developed severe pancytopenia in spite of giving several units of blood products and after the stoppage of suspecting antibiotics. We did a bone marrow aspiration which showed dilute marrow with occasional

scattered normoblast, scattered myeloid cells and absent megakaryocytes. The trephine biopsy showed severe aplastic anaemia with the marrow cellularity around 10%. He then became clinically better and his coagulation parameters returned to normal. His blood counts were monitored and after one month, the bone marrow was repeated which showed a remarkable recovery with 50-60% cellularity and normal trilineage hematopoiesis. Blood parameters also became normal.

**Discussion:** This patient has a rare manifestation of snake bite producing severe aplastic anaemia. He was lucky to have a reversible Bone Marrow aplasia which is not common to normalize in the short period of time without specific treatment. It may be better to keep the patient on a long term follow up as many other similar circumstances (like drugs, chemicals, infections etc) could lead to a suppression of Bone Marrow in this patient again. The variation in the constituents in the snake venom accounting for this phenomenon could be possible. Any unusual constituent which could have suppressed the bone marrow temporally either directly or through immunological mechanisms. What that particular unusual constituent was, remains a mystery.

### **AAPI-22-007-PO: Epidural Blood Patch Treatment for Headache caused by Slow-leaking Tarlov Cyst**

**Chandrasekar EK, Kent J.** University of Rochester Medical Center, Rochester, NY, USA

**Background:** Tarlov cysts are cerebrospinal fluid (CSF) filled sacs that are most commonly in the sacral region. While usually asymptomatic, rupture of Tarlov cysts is associated with intracranial hypotension.

**Case Description:** We present a 74-year-old female who was referred to our pain center for positional headache and tinnitus. Her MRI showed multiple thoracic nerve root sheath cysts, notably at T5-T6 and T6-T7, and extradural CSF signal without acute cyst rupture, most consistent with slow leak. She receives thoracic blood patches every 3 to 6 months to maintain 90-100% relief of symptoms.

**Discussion:** This is one of the first documented cases of slow-leaking Tarlov cyst causing symptoms of intracranial hypotension.

### **AAPI-22-008-PO: A Rare Presentation of Spina Bifida Occulta in Post-dated Pregnancy with Oligohydramnios - Case Report**

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**Background:** Neural tube defects (NTDs) are congenital anomalies of the central nervous system affecting every 1 in 1000 pregnancies. The causes include failure of neurulation happening around the 28th day after conception, non-compliance to folic acid supplements, and consumption of antiepileptic medication during pregnancy. Spina bifida is the most common malformation of the spine, in which failure of fusion of posterior laminae of vertebrae occurs with or without developmental defect of the spinal cord. Based on the presentation, such cases are classified as occulta (mild type) or cystica (severe form including meningocele and meningomyelocele).

**Case Description:** A newborn female, delivered at 42 weeks of gestation, presented with mild respiratory distress and tufts of hair on the back. Polydactyly was also present. On review of history, her mother had no prenatal care, as she never visited the hospital during her antenatal period and did not take folic acid supplements. Ultrasonography taken before labor revealed severe oligohydramnios, a common manifestation of post-dated pregnancy. Upon labor induction, the baby was born appropriate for gestational age with a poor cry and Apgar scores of 5 and 8 at 1 min and 5 min. The newborn was transferred to neonatal intensive care unit and oxygen supplementation was provided via hood. X-ray taken 1-day post-delivery showed gibbus deformity of spinal vertebrae at the level of T7-L2. Neurologist opinion was obtained.

**Discussion:** Usually, Spina Bifida occulta cases are asymptomatic. It is also associated with lower joint deformity, club foot, scoliosis, hydrocephalus, and brain damage. Diagnostic tests include prenatal AFP screening, ultrasound, amniotic fluid tests and imaging studies. In this case, the presence of polydactyly and gibbus deformity suggests strong genetic/infectious etiology. Association of polydactyly in spina bifida is rarely found in the literature. Further studies are required to rule out the prevalence of such cases.

### **AAPI-22-009-PO: Recurrent Hypoglycemia, Shortness of breath, and a Fibrous Tumor Leading to Near Full Atelectasis: Masks of Doege-Potter Syndrome**

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**Background:** Doege-Potter syndrome is a rare paraneoplastic syndrome presenting as a hypo-insulinemic hypoglycemia from the ectopic secretion of a pro-hormone of insulin-like growth factor II (IGF-II) from a solitary fibrous tumor [1]. Delay in diagnosis can result in episodes of hypoglycemia which could lead to syncopal episodes and even cerebral injury. Being a rare disease entity, it can be overlooked as episodes of hypoglycemia. We are reporting a case of Doege-Potter syndrome in 61-year-old woman.

**Case Description:** A 61-year-old female presented with complaints of recurrent episodes of vertigo, uneasiness followed by syncope with mild shortness of breath with left sided chest heaviness for the last 6 months. Patient was asymptomatic 6 months ago when she developed sudden onset vertigo, uneasiness with profuse perspirations followed by a syncopal episode for which she was hospitalized locally. She had profound hypoglycemia without any history of diabetes mellitus, hypoglycemic medications, or family history. Patient took discharge against medical advice and subsequently, presented with 3 similar episodes at the local hospital before presenting to our hospital.

**Discussion:** With Dextrose infusions and regular blood sugar charting, the recurrent hypoglycemia was unmasked. Dullness on percussion and HRCT chest revealed a Left Lung mass occupying the left hemithorax. C-peptide levels were low and IGF-2 levels were elevated which suggested the diagnosis. The diagnosis was confirmed after biopsy of the mass which revealed a fibrous tumor. Patients made full recovery after surgical excision of the tumor. Shortness

of breath could be a presentation in pleural variety of tumors. Doege-Potter Syndrome should be kept as a differential for patients presenting with recurrent hypoglycemia. As with surgical resection of tumor the prognosis is excellent. Shortness of breath could be a presentation in pleural variety of tumors.

### **AAPI-22-010-PO: Hereditary Hemorrhagic Telangiectasia in a Ghanaian Adult Male - A Case Report**

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**Background:** Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu disease, is a rare autosomal dominant disease, affecting multi-organ systems characterized by mucocutaneous and visceral telangiectasia as well as arteriovenous malformations (AVMs). This disorder has been reported to be rare in people of black African descent but common in Caucasians. To the best of our knowledge, this is the first reported case in the literature of a definite hereditary hemorrhagic telangiectasia diagnosed in Ghana, a resource-limited setting with limited treatment options.

**Case Description:** Our patient is a 30-year-old Ghanaian male who presented to our hospital's emergency department with a complaint of occipital headache and epistaxis. He's had recurrent nose bleeds since childhood. His physical examination revealed telangiectasia on the lower lip and tongue. The father has episodic nose bleeds, his 2 older half-sisters have spontaneous nose bleeds, his twin brother has episodic nose bleeds, one-half of his twin sister and younger male sibling has spontaneous nosebleed. A non-contrast head CT scan revealed intracerebral hemorrhage and a CT scan with angiogram showed cerebral arteriovenous malformations. He fulfilled the Curacao diagnostic criteria for definite hereditary hemorrhagic telangiectasia. Treatment options were unavailable in this setting, and the patients' GCS suddenly dropped with low saturation. He was intubated but ultimately had a cardiac arrest with pulseless electrical activity and died despite multiple attempts at cardiopulmonary resuscitation.

**Discussion:** This rare case of hereditary hemorrhagic telangiectasia has shown that it occurs in an African population and that diagnostic challenges in resource-limited settings poses a major challenge. Due to its fatal complications, early diagnosis is paramount in initiating preventive screening and surveillance since treatment options also remain a challenge in these settings.

### **AAPI-22-011-PO: A Study of the Factors Influencing Knowledge, Attitude and Practice of Physicians and Nurses in Breaking Bad News to Cancer Patients at Black Lion Specialized Hospital, Addis Ababa, Ethiopia**

Regassa H<sup>1</sup>, Sindu D<sup>2</sup>, Messele L<sup>1</sup>, Ephrem N<sup>3</sup>, Geleta A<sup>3</sup>, Gulelat M<sup>1</sup>, Mulugeta E<sup>4</sup>, Mekuria Z<sup>1</sup>. <sup>1</sup>St.Paul's Hospital Millennium Medical College (SPHMMC), Ethiopia; <sup>2</sup>Sree Gokulam Medical College & Research Foundation, Venjarammoodu, India; <sup>3</sup>All African Leprosy, Tuberculosis and Rehabilitation and Training Center, Ethiopia; <sup>4</sup>Addis Ababa University College of Health Sciences School of Medicine, Ethiopia.

**Background:** Delivering unexpected news to patients is one of the most challenging tasks undertaken by healthcare practitioners. It plays a significant role in the process of treatment and patient cooperation.

**Objectives:** To gain an understanding of the knowledge, attitude, and practice of healthcare practitioners regarding breaking bad news and its impact on patient care.

**Methods:** A cross-sectional study was conducted at Black Lion Hospital from May 1 to July 30, 2021. A simple random sampling technique was used to select the participants of the study. The questionnaires were standardized and self-administered by the participants. The data collected was entered in to the Epidata software versions 3.1, then imported to SPSS version 25.0 to perform descriptive statistics and other analysis.

**Results:** Among the participants, 13.8% were not trained to deliver unfavorable news to patients. Lack of training and workload were the main hinderances in delivering such news. Additionally, 47.2% of the participants scored greater than 75% in communicating bad news to cancer patients. Meanwhile, 72.2% of the practitioners scored greater than 50% on the Clark and Watson scale for

attitude of physician towards breaking bad news whereas only 33% of the participants scored greater than 75% on the Clark Watson practice questioner. One in four participants is confident in his/her ability to break bad news to their patients.

**Conclusion:** This study aims to identify key factors influencing the knowledge, attitude, and practices of healthcare practitioners in delivering unfavorable news to cancer patients. It indicated, while a large proportion of the practitioners had favorable attitudes, they had poor knowledge and practices based on the SPIKES protocol. Institutions can use this research to guide future training of physicians and nurses and improve the quality-of-service delivered at their respective institutions.

### **AAPI-22-012-PO: The Incidence of Cardiomyopathies Among Athletes in Developing Countries and the Prevention Strategies**

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**Background:** Incidence of cardiomyopathies in athletes contribute significantly to the public health burden in developing countries. Limited data is available concerning the incidence of adverse events related to cardiomyopathies amongst athletes in developing countries. Most effective strategies primarily rely on the modification of risk factors; however, it is less expensive compared to other advanced investigations.

**Objective:** To discuss the incidence of major adverse cardiac events in athletes with cardiomyopathies and their associated risk factors. The article aims to evaluate the various strategies proposed to prevent the progression of cardiomyopathies in this population.

**Methods:** A comprehensive search strategy was used to screen and identify any relevant literature. This was done in accordance with the PRISMA workflow. Risk of bias

assessment was completed through the Newcastle-Ottawa scale for case-control and cohort studies.

**Results:** Four studies were identified in the final analysis. The incidence of sudden cardiac arrest varied between 0.3 to 0.33% among the athletes affected with cardiomyopathies. Routine and Pre-participation screening has shown success in reducing the incidence of sudden cardiac death in athletes as a result of undiagnosed cardiomyopathies. Supervised exercise regimes have been proposed to reduce the incidence of cardiomyopathy in athletes. Beyond identification strategies, prevention of cardiomyopathies revolves around the modification of risk factors. This involves screening for cardiovascular events in athletes and their associated risk factors. The studies showed a low-moderate risk of bias.

**Conclusion:** The challenges athletes face, suffering from cardiomyopathy, has been an ongoing issue with unexpected cardiac arrest as the end result. Despite the decreased incidence of cardiomyopathies observed in athletes, the challenge in diagnosis can result in catastrophic outcomes, especially in developing countries. Therefore, adopting prevention strategies can have a profound impact on the identification and management of these pathologies.

### **AAPI-22-013-PO: Factors Impacting Adherence to Anti-hyperglycemic Medications in Adults with Type 2 Diabetes at St. Peter's Specialized Hospital, Addis Ababa, Ethiopia**

**Regassa H<sup>1</sup>, Sindu D<sup>2</sup>, Messele L<sup>1</sup>, Birhanu B<sup>3</sup>, Birahnu M<sup>3</sup>, Gulelat M<sup>1</sup>, Mulugeta E<sup>3</sup>, Mekuria Z<sup>1</sup>, Nigusse B<sup>4</sup>, Habtamu A<sup>1</sup>.** <sup>1</sup>St.Paul's Hospital Millennium Medical College (SPHMMC), Ethiopia; <sup>2</sup>Sree Gokulam Medical College & Research Foundation, India; <sup>3</sup>All African Leprosy, Tuberculosis and Rehabilitation and Training Center, Ethiopia; <sup>4</sup>Columbia University New York, USA.

**Background:** The prevalence of type 2 diabetes (T2D) in low-income countries has increased substantially resulting significant long-term socioeconomic impacts.

**Objectives :** This study examines factors impacting non-adherence to anti-hyperglycemic medications in adults with T2D at St. Peter's Specialized Hospital in Addis Ababa, Ethiopia from July 1 to July 30, 2021.

**Methods:** Systematic sampling techniques were used to select the sample size, and a structured interview was conducted to collect data on patient medication adherence. The data were entered into the Epi-Info version 7 (Centers for Disease Control and Prevention, Atlanta, USA) and analyzed using analytical statistics such as frequency, central tendencies, odds ratio, binary logistic regression, and multiple logistic regression models to summarize the results. We considered  $p < 0.05$  as statistically significant.

**Results:** Three hundred eleven patients participated in the study, with 204 (65.6%) men and 107 (34.4%) women and a mean age of 48.5 years (standard deviation: 15 years). Most patients were older than 60 (27.7%), and 25.1% were aged 41 to 50. We found that 25.7% of patients were non-adherent to their anti-hyperglycemic medications (95% confidence interval: 20.3, 30.9). Factors associated with non-adherence were ages 31 to 40 and 51 to 60, being single, being self-employed, and working as a farmer.

**Conclusion:** This study evaluates the magnitude of non-adherence to anti-hyperglycemic medications and the associated factors in adult T2D patients. Approximately one in four participants were non-adherent to their anti-hyperglycemic regimen despite free access to such medications, primarily because they felt better, but some stopped due to feeling worse after ingesting the medications or inconvenience. Additionally, age of the respondent, marital status, and occupation were the independent factors associated with anti-hyperglycemic medication non-adherence. The findings may be of interest to other African countries with growing rates of T2D and aid in the improvement of future management of these patients.

### **AAPI-22-015-PO: Renal Artery Angioplasty in Takayasu Disease – Difficult Anatomy Addressed with a Novel Technique**

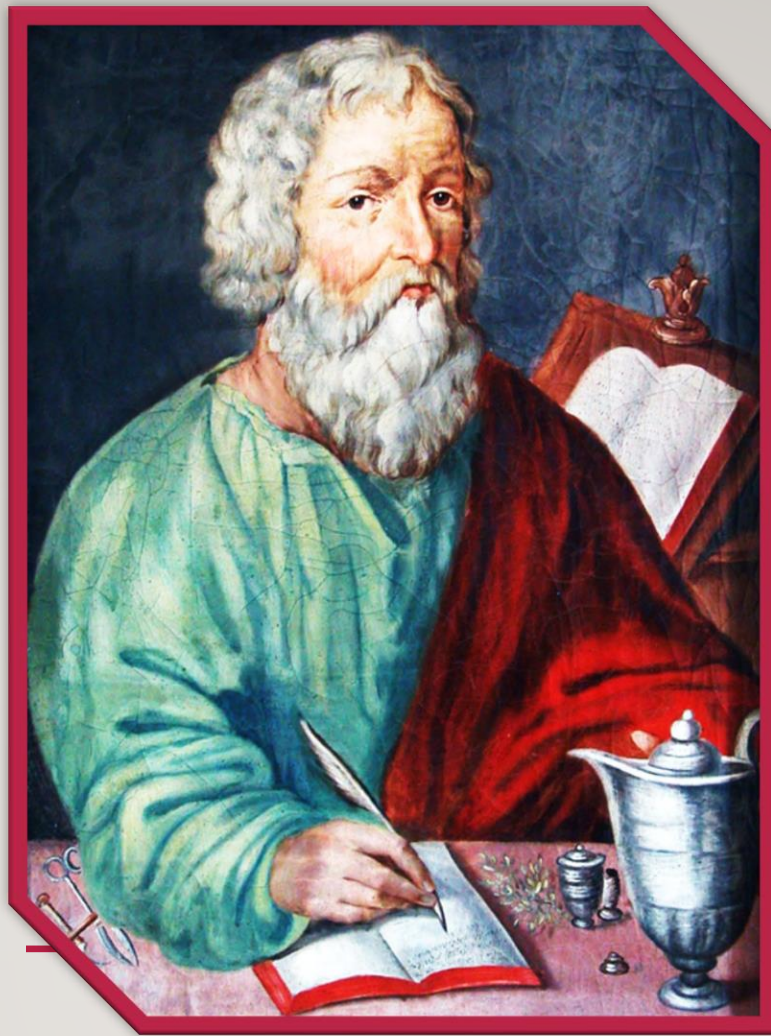
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**Background:** TA is a rare chronic inflammatory and granulomatous vascular disorder affecting large arteries of the body which is prevalent in Asian countries affecting women before the 4th decade of life and is the most common cause of reno-vascular hypertension in India. First line management of TA includes drug therapy but in cases with vascular complications, interventions and revascularization procedures are the mainstay.

**Case Description:** Various anatomical and technical difficulties encountered during percutaneous transluminal balloon angioplasty (PTRA) in a case of takayasu arteritis (TA) necessitated an innovative interventional approach, followed by placement of a coronary drug eluting stent (DES) in the left renal artery using a novel technique.

**Discussion:** PTRA is a time-tested procedure in treating TA induced renal artery stenosis with technical and clinical success rates reaching up to 95% and 89% respectively with reduction in stenosis and anti-hypertensive therapy. However, restenosis (rate  $\approx$  18%) continues to be the main challenge till date. Clinical evidence suggests that DESs are superior to bare metallic stents (BMSs) for achieving better renal function. This case appears to be one of the first few documented cases of DES implantation in a young female patient affected with TA. The different hardware and techniques used in this case have not been used earlier in performing PTRA in TA patients with such technical difficulties.





Portrait of Hippocrates (1787), by the  
Majorat of Setúbal.  
Image in Public Domain

**Science is the father of knowledge,  
but opinion breeds ignorance.  
- Hippocrates**