

JAAPI

Journal of the American Association of Physicians of Indian Origin

ISSN: 2769-2620 (Print) & 2769-2639 (Online) Vol. 1 No. (1) Spring 2021



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

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This Inaugural Issue of JAAPI is Dedicated to the following Legendary Indian Physicians



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Sushruta (600 BCE) Father of Plastic Surgery

Rhinoplasty, Dentistry, Ophthalmology,
Anatomy, Pathophysiology and Therapeutic
Strategies

Recognized obesity as a disease and linked it
to diabetes and heart diseases.

Champaneria et al, Ann Plastic Surgery 2014
<https://pubmed.ncbi.nlm.nih.gov/23788147/>

Bath et al, J Med Biogr, 2019
<https://pubmed.ncbi.nlm.nih.gov/27885151/>

Dr. Yellapragada Subbarow (1895 – 1948) The Man of Miracle Drugs

The first Indian Medical Doctor who stepped on
American soil in modern times, and left an
indelible mark in medical research with
groundbreaking discoveries in multiple fields -
from megaloblastic anemia to tropical diseases
to antibiotics to cancer therapy to metabolism.

*You've probably never heard of
Dr. Yellapragada Subbarao, yet because he
lived you may be well and alive today; because
he lived you may live longer.*
- Doron K. Antrim – Author & Editor

An Indian Scientist in America

http://www.ccras.nic.in/sites/default/files/viewpdf/jimh/BIJHM_1976/128%20to%20143.pdf



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JAAPI is a Publication of the
American Association of Physicians of Indian Origin (AAPI)
600 Enterprise Dr., Suite 108, Oak Brook, IL 60523
<https://www.aapiusa.org/>

The views expressed by the authors do not necessarily reflect those of the AAPI.



AMERICAN ASSOCIATION OF PHYSICIANS OF INDIAN ORIGIN

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Message of the President of AAPI Dr. Sudhakar Jonnalagadda

April 27, 2021

I'm so proud to see the birth of the Journal of AAPI (JAAPI), a purely scientific publication destined to be a major influence in medical education. Congratulations to Dr. BK. Kishore and his team, who have envisioned, planned, and tirelessly strived to give us a journal of which we will all be so immensely proud.

AAPI has grown to 80,000 physicians, and it is time for a journal dedicated to the success and education of our members, especially our younger physicians. JAAPI will provide not only strong educational materials, but also opportunities for enhanced learning through deep interaction. AAPI support for this Journal will be crucial. I urge you to do your part to eagerly read, discuss, and contribute to each issue of JAAPI.

I thank AMA President Dr. Susan Bailey for launching our JAAPI.

Best Wishes

Sudhakar Jonnalagadda, M.D., AGAF

President, AAPI



The Executive Committee and Board of Trustees of AAPI, and the Editorial Board of JAAPI Express their Gratitude to the Following Distinguished Physicians and Scientists for their Support to JAAPI.

Susan R. Bailey, M.D.

President, American Medical Association
For Launching and Felicitating JAAPI

Peter C. Agre, M.D.

Nobel Laureate in Chemistry 2003
Bloomberg Distinguished Professor and Director
Johns Hopkins Malaria Research Institute
For Felicitating JAAPI

Mario R. Capecchi, Ph.D.

Nobel Laureate in Medicine or Physiology 2007
Distinguished Professor of Human Genetics
University of Utah Health
For Felicitating JAAPI

Mitchell S.V. Elkind, M.D., MS

President, American Heart Association
Professor of Neurology & Epidemiology, Columbia University
For Contributing an In-depth Review Article

D. Nageshwar Reddy, M.D., D.M., D.Sc.

Director, Asian Institute of Gastroenterology and
Crystal Awardee, American Society for Gastrointestinal Endoscopy
For Contributing a State-of-the-Art Review Article



SUSAN R. BAILEY, MD

PRESIDENT

susan.bailey@ama-assn.org

ama-assn.org

t (312) 464-4016

t (817) 315-2550 ext. 206

April 19, 2021

B.K. Kishore, MD, PhD, MBA
Editor-in-Chief
Journal of AAPI

Dear Dr. Kishore,

On behalf of the American Medical Association, I congratulate you and the Editorial Board of the Journal of the American Association of Physicians of Indian Origin on the occasion of its launch. I am confident that JAAPI will become an invaluable and trusted source for scientific study and health care information for a wide range of users, including practicing and academic physicians, residents and interns, medical school students and many others.

You are embarking on an important mission at JAAPI to gather the collective knowledge and hands-on experience of subject matter experts in a range of medical fields, and share these insights and experiences with physicians around the world.

I believe, as you do, that this undertaking will allow JAAPI to reinforce the mission of its parent organization to promote professional solidarity in the pursuit of excellence in patient care, teaching and research.

I congratulate you on this important addition to the ranks of our nation's leading peer-reviewed medical journals. I look forward reading JAAPI in the months and years ahead.

Sincerely,

Susan R. Bailey, MD



Susan R. Bailey, M.D. President American Medical Association

Dr. Susan R. Bailey, a distinguished Allergist/Immunologist from Fort Worth, Texas, is the 175th president of the American Medical Association.

A fierce advocate for physician autonomy and private practice, Dr. Bailey has held numerous leadership positions with the AMA, including serving as Speaker and Vice Speaker of the AMA's House of Delegates; Chair of both the Advisory Panel on Women in Medicine and the AMA Council on Medical Education. She has also represented the AMA on the Accreditation Council for Continuing Medical Education, the American Board of Medical Specialties, and COLA.

Her dedicated service in organized medicine extends to the local and state levels, where she has served as Chair of the Board, and President of the Tarrant County Medical Society, and as Vice Speaker, Speaker and President of the Texas Medical Association.

Dr. Bailey has been an allergist in private practice for over 30 years. She completed her residency in General Pediatrics and a Fellowship in Allergy/Immunology at the Mayo Graduate School of Medicine in Rochester, Minnesota, and has been awarded the title of Distinguished Fellow of the American College of Allergy, Asthma, and Immunology.

In addition to receiving her medical degree with honors from the Texas A&M University College of Medicine, Dr. Bailey was later appointed to the Texas A&M System Board of Regents by then-Gov. George W. Bush, and has been named a Distinguished Alumnus of Texas A&M University and of Texas A&M University College of Medicine.



Women Leadership in Medicine with Dr. Susan Bailey and Dr. Margaret Ferguson Mar 19, 2021

<https://www.youtube.com/watch?v=oJhsMl1inAg>



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JOHNS HOPKINS
U N I V E R S I T Y

Bloomberg School of Public Health

Department of Molecular Microbiology and Immunology
615 N. Wolfe Street / Baltimore MD 21205-2179
443-287-8743 / pagre@jhu.edu

Peter Agre, MD
Bloomberg Distinguished Professor and Director
Johns Hopkins Malaria Research Institute

05 February 2021

My compliments to the AAPI (American Association of Physicians of Indian Origin) on the launching of the peer-reviewed JAAPI (Journal of AAPI) and to its Editor-in-Chief, Prof. Bellamkonda K. Kishore, M.D., Ph.D., MBA, FASN, FRSB, FAPS, FAHA, The University of Utah. In this information age, it is important to have clear lines of communication.

Sincerely,



Peter Agre, M.D.
Bloomberg Distinguished Professor and Director
Johns Hopkins Malaria Research Institute
Nobel Laureate in Chemistry 2003



Pioneers in Medicine and Healthcare

Prof. Peter C. Agre, M.D.

Co-Winner of Nobel Prize in Chemistry 2003

Bloomberg Distinguished Professor

Director, Johns Hopkins Malaria Research Institute

Johns Hopkins Bloomberg School of Public Health

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Chance Favors the Prepared Mind – Louis Pasteur

It was late 1980s. Venue, Johns Hopkins School of Medicine in Baltimore, Maryland. **Peter Courtland Agre, M.D.**, a Hematologist by training and a Professor of Medicine and Biological Chemistry, was stuck with an unusual finding. Sitting in his office, once occupied by Dr. Albert L. Lehninger, the legendary biochemist, Dr. Agre was deeply contemplating. He had a gut feeling he stepped on something phenomenal. But little did he realize that he would come up with a groundbreaking discovery in biology and medicine. As a Hematologist, his interest was studying rare blood group proteins. His lab was extracting proteins from human red blood cell membranes and separating them on polyacrylamide gels. They were consistently finding a particular band of about 28 kDa size showing up in the gels. What was bothering Dr. Agre, this unknown protein constituted 4% of the total membrane proteins, which was high, unless it has a major functional significance. Being a researcher of persistent nature, Dr. Agre kept on probing it further. His lab isolated this protein in pure form, and derived its corresponding cDNA from bone marrow by RT-PCR using degenerate primers. They hypothesized that it must be a membrane channel transporting water and/or other molecules, because red blood cells are known to be resistant to rapid changes in osmolality while passing through different tissues. Experiments on *Xenopus* (frog) oocytes where they injected cRNA for the protein brought out the Eureka moment. Dr. Peter Agre and his group discovered and cloned the first water channel. Dr. Agre named it as CHIP28 (**Ch**annel **F**orming **I**ntegral **P**rotein of 28 kDa), now called Aquaporin-1. The rest was history. Now we know a whole family of aquaporin water channels in animals. We also know corresponding water channel molecules in bacteria, algae, and plants. Not only that the discovery and characterization of aquaporin water channels made it possible to understand the physiology of water homeostasis and pathophysiology of disorders of water balance. Sometimes, these enabled designing of rational approaches to correct or treat disorders of water balance. Our understanding of water as a biological element essential for life is made possible due to the discovery of aquaporins and the ensuing molecular physiology of water homeostasis.

In recognition of his groundbreaking discovery, in 2003 Dr. Peter Agre shared Nobel Prize in Chemistry with Dr. Roderick McKinnon for their contributions on ion and water channels. Dr. Agre does not rest with a Nobel Prize. His commitment for science, medicine and humanity is unlimited. After receiving the Nobel Prize he served as the President of the American Association for the Advancement of Science (AAAS). During that period he initiated **Science Diplomacy** and toured countries like North Korea and Cuba, where government diplomats are not allowed. Dr. Agre was received by the heads of states and scientific community of those totalitarian regimens with warmth and friendship due to his commitment to science and humanity. Dr. Agre believes that science can unite countries where governments could not.

After his tenure at the AAAS, Dr. Agre returned to the Johns Hopkins Bloomberg School of Public Health as the Director of Malaria Research Institute. One in every two persons ever contacted malaria dies due to the disease. Dr. Agre believes that the solution for malaria eradication lies in understanding the biology and vulnerability of the mosquito, the malaria vector. So, his lab is studying the biology of female *Anopheles* mosquitoes. Sooner or later, they may come up with another major discovery on how to break the connection between the malarial parasite and the humans by neutralizing the vectors. Such is the caliber, dedication and commitment by Dr. Peter Agre.

Peter Agre at TEDMED 2011 <https://www.youtube.com/watch?v=-eq5tfU1kZY>

The Human Side of a Life in Science at TEDxMidAtlantic <https://www.youtube.com/watch?v=x4LP9m98obw>

Article Contributed by: Bellamkonda K. Kishore, M.D.

February 25, 2021

B. K. Kishore, M.D., Ph.D., MBA
Editor-in-Chief
Journal of AAPI

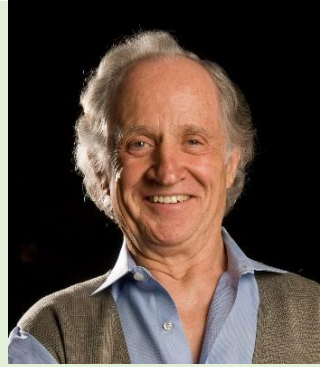
Dear Dr. Kishore,

I compliment the American Association of Physicians of Indian Origin (AAPI) on the occasion of launching JAAPI, a peer-reviewed medical and healthcare journal of AAPI. I wish a very successful launching and growth of JAAPI as a valuable source of information and knowledge to practicing clinicians and academic physicians as well as junior doctors in training. JAAPI is definitely a feather in the cap of AAPI. I thank Prof. Bellamkonda Kishore, my fellow faculty at University of Utah Health, for taking responsibility as the Editor-in-Chief of AAPI.

Sincerely,



Mario R. Capecchi
Distinguished Professor
University of Utah School of Medicine
Department of Human Genetics
Nobel Laureate in Medicine or Physiology 2007



Pioneers in Medicine and Healthcare

Prof. Mario R. Capecchi, Ph.D.

Co-Winner of Nobel Prize in Physiology or Medicine 2007

Distinguished Professor of Genetics and Biology
University of Utah School of Medicine
Salt Lake City, Utah, USA

We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this must be attained. – Marie Curie

Today, knocking out or knocking in or overexpressing or altering a gene in an intact animal is a routine genetic engineering technique. But when it was designed and performed for the first time, it was as sensational as the birth of the first test tube baby or first cardiac transplantation. Behind such groundbreaking and game-changing technological developments, there were great men and women of exceptional abilities, skills, dedication and above all a spirit of human endeavor to conquer the nature and nurture the humanity into a new realm of existence. And some might have struggled with innumerable difficulties while they were young. An illustrious personality of that caliber is **Prof. Mario Ramberg Capecchi**, who was a Co-Winner of Nobel Prize in Physiology or Medicine in 2007, along with Sir Martin J. Evans and Oliver Smithies.

Born in Italy in 1937 as the only child of his parents, Dr. Capecchi had a traumatic childhood during World War II. His father, an airman, was reported missing in action. His mother was sent to a concentration camp as punishment for distributing anti-fascist pamphlets. Although she arranged with a peasant family to provide for her son during her absence, after one year the money she gave was exhausted, leaving her son without care. As a child of four-and-half years old, little Mario was left on the streets of Northern Italy fending for himself, moving from one orphanage to another, and living with homeless children on the streets for the next four years. He almost died of malnutrition. Finally, his mother, having been released from the camp, found her son in a hospital bed suffering from fever and sustaining on bread crumbs. She took him to Rome, where he had his first decent bath after six years. In 1946, Edward Ramberg, the uncle of Mario and an American Physicist at the Radio Corporation of America, sponsored his sister and her son to migrate to the United States. The rest was history. In 1961 Mario Capecchi graduated with B.S. in Chemistry and Physics, and in 1967 obtained his Ph.D. in Biophysics from the Harvard University, working under the mentorship of James D. Watson, the co-discoverer of the structure of DNA. In 1973, Dr. Capecchi joined the faculty at the University of Utah in Salt Lake City, where he continues his research as a Distinguished Professor of Genetics and Biology even at 83 years.

Dr. Capecchi won the Nobel Prize along with Martin Evans and Oliver Smithies for their contributions in creating the first gene knockout mouse by genetic engineering and in vitro fertilization, where a selected gene was turned off or inactivated. However, when Dr. Capecchi first proposed this in his NIH grant application, the reviewers apparently turned it down stating "it is impossible". That speaks volumes on the task before the young Dr. Capecchi and his determination to knockout a gene. Genetic engineering has changed the way we understand the disease processes and how we treat them. With CRISPR/Cas9 or gene editing technology, today we are at the verge of entering new horizons of clinical medicine whereby we can treat not only genetic diseases in adults, but also prevent the birth of babies with defective genes due to familial genetic abnormalities. In about a decade or less, genetic engineering becomes part of the Personalized Medicine. All these are possible due to determined scientists, such as Prof. Mario Capecchi, who brought out the best in themselves and gave it to the humanity, despite the harsh conditions they had to face in their early lives.

Modeling Neuropsychiatric Disorders in the Mouse | Mario Capecchi | TEDxGeorgeSchool

https://www.youtube.com/watch?v=X_t0_56njGw

Article Contributed by: Bellamkonda K. Kishore, M.D.

Editorial

Elevating AAPI to New Heights through JAAPI

Bellamkonda K. Kishore, M.D., Ph.D., MBA

Editor-in-Chief of JAAPI

Correspondence: jaapi@aapiusa.org

*The glory of medicine is that it is constantly moving forward, that there is always more to learn.
The ills of today do not cloud the horizon of tomorrow, but act as a spur to greater effort.
– William James Mayo, M.D.*

The doctors who save lives of their patients are not always made in medical schools. They often create themselves through diligent practice of Evidence-based Medicine in the community. The real test a doctor faces is not the one administered in the medical school, but the one s/he has to face when standing between the life and death of patients. What empowers a doctor in those critical moments is right knowledge, despite technological superiority of modern medicine - *Knowledge is Power of the Noble Profession that has the potential to elevate a Nation.*

While standard textbooks can help medical students to pass exams, their use soon evaporates once students are out to practice medicine in the community. Today the problem faced by many physicians is not dearth, but plethora of information with no readily available algorithms to navigate through, digest, and assimilate new information which is not well-organized like in the textbooks. Discussing with a knowledgeable senior colleague has become a tradition of the past, even to those who are in academia. Clinical grand rounds, journal clubs, and seminars are useful, but may not be accessible to all physicians. The high-impact medical journals provide the latest information. But the depth and breadth of their articles are not compatible with busy lifestyle of physicians. Under such circumstances a budding doctor or establishing physician on a learning curve asks one question – *Where can I obtain the right information in a concise and easy to assimilate manner?*

It is possible to create such a source, if well-trained physicians and academicians contribute their accumulated knowledge combining with the latest information so it meets the needs and expectations of physicians. The launching of JAAPI is a step in that direction. We anticipate JAAPI to become a unique peer-reviewed journal that seamlessly bridges the knowledge gap between clinical practice and evidence-based medicine in a simple and easy-to-follow manner, although empowering physicians with knowledge is not simple always. Because, as Neil deGrasse Tyson, the Astrophysicist and Educator said: *One of the great challenges in this world is not knowing enough about a subject to think you are right, but not enough about the subject to know that you are wrong.* So, the real challenge is how to impart right amount of knowledge that empowers physicians to discern what is right and what is not right, without overwhelming with information. Yes, it is possible through journals like JAAPI, where experts in the field extract, filter, process, and present complex subjects in easily discernible fashion with the right amount of knowledge. In this context, JAAPI is not just a peer-reviewed journal. *It acts like a conduit channeling the collective knowledge and experience of experts in various fields to physicians.* Thus, JAAPI strengthens the Vision of AAPI – *To promote professional solidarity in pursuing excellence in patient care, teaching and research.* As medical professionals, we have reached a point where medical education and healthcare delivery are dependent more on innovative opportunities each one of us creates for the collective growth of the nation than on federal or state dollars spent. This is the fact the immigrant Mayo family realized 170 years ago when they created Mayo Clinic, *a nonprofit organization with a mission of inspiring hope and promoting health through integrated clinical practice, education, and research.* By aspiring for a high mission, JAAPI helps us to elevate AAPI to new heights.

Either write something worth reading or do something worth writing about. – Benjamin Franklin

JAAPI: Through the Lens of Its Editors

The beginning of JAAPI was a collective simmering of those who felt the need to create a platform to express and share their curiosity in professional and scholarly activities. AAPI mission statement states “AAPI is a forum to facilitate and enable Indian American Physicians to excel in patient care, teaching and research and to pursue their aspirations in professional and community affairs”, as such we invite every one of you to board the JAAPI flight, spread your wings, and join the ensemble of scholarly activity and publication chorus. Research ignites the log of inquisitive mind and keeps burning while emanating the warmth of scholarliness. To believe in truth is sublime while to prove is even more arduous and research embraces both. We at the AAPI Editorial Board envision that within the sea of diversity among the AAPI members there are those doused in a wealth of academic, research and scholarly sojourn needing a platform to express their innate desire within our organization. JAAPI will provide an opportunity to bring the collective thinking and share them with the members of AAPI and the world. The Editorial Board had worked diligently over several months to unfurl the first issue of JAAPI and it hopes JAAPI to become a premier journal of medicine of the future.

With the exemplary leadership and tireless work of Editor-in-Chief Dr. Kishore and ably supported by AAPI leadership we are on the historic verge of releasing the peer-reviewed journal JAAPI. In this context, Hungarian born American Nuclear Physicist Edward Teller's quote is apt: *A fact is a simple statement that everyone believes. It is innocent, unless found guilty. A hypothesis is a novel suggestion that no one wants to believe. It is guilty, until found effective.*

Raj Alappan, M.D., FACP, FCCP, FASN
Deputy Editor
Nephrologist

There is a long history of Indian healers (physicians) in taking care of people in need since the days of legendary healers like Susruta and Charaka. Since, then Indian born physicians and scientists, made a great impact in health and wellbeing of people across the world. These efforts of dedicated physicians are extraordinary and exemplary. Despite the fact that there is brain drain from India, Indian born physicians found unique niche in personal and professional growth and taking care of patient ailments across the world. Unselfish sharing of their wisdom and unconditional healing power to the humanity is making a strong impact in the world and making our country of origin proud. In order to make an organized impact at a national and international level, there is momentum through our great organization, AAPI, we are proud to start a medical journal JAAPI. It is my immense pleasure and honor to be part such a great organization and Editorial Board member of JAAPI. It is being organized and lead by extraordinary and tireless scientific leader and Editor-in-chief Dr. Bellamkonda Kishore and excellent group of Deputy Editors and Editorial Board Members. I believe JAAPI will be instrumental in bringing and encouraging talents of physicians and scientists across the world and to be more specific, a great platform for Indian born students, residents, fellows, practicing physicians and scientists. I am proud to be part of this great scientific endeavor and grateful for the opportunity to serve and contribute to science, through JAAPI.

Sreenivas Chandana, M.D., Ph.D.
Deputy Editor
Hematologist & Oncologist

I am honored to be a part of JAAPI under the guidance of Dr. Kishore and the AAPI Leadership Team. As the largest group of South Asian American physicians in the United States, AAPI sets the tone for doctors of Indian origin to strive towards excellence. The creation of a peer-reviewed journal will add credence to the professional aspects of organization and encourage AAPI physicians and student members to take a more active role in scientific research and publications.

Kavitha Das, BDS, MPH, MS
Deputy Editor
Senior Scientist in Cardiology

Twenty-five percent of all physicians in the USA are international medical graduates (IMG), and they are vital to the health and wellbeing of all Americans. Physicians of Indian origin constitute the largest group of IMGs practicing in the USA. American Association of Physicians of Indian Origin (AAPI) was started in 1982 with a mission to facilitate and enable Indian American Physicians to excel in patient care, teaching, and research. The launching of the peer-reviewed Journal of the AAPI (JAAPI) furthers the academic goals of AAPI. We hope JAAPI provides a platform for young and established scientists and physician investigators from around the world, not just of Indian origin, to publish their research results. This huge effort resulted from the visionary leadership of the AAPI and the tireless efforts of the Editor-in-Chief. We are thankful for their foresight and hard work. As someone who has spent over 40 years in academic medicine, I am thankful to them for the opportunity to serve on the Editorial Board of the JAAPI.

Ramasubbareddy Dhanireddy, M.D.
Deputy Editor
Neonatologist

I am honored and feel privileged to be part of JAAPI. It is rarely (in medicine) that one gets to be part of a "startup". In my humble opinion, the creation of JAAPI is the best idea of AAPI. I have always been proud of my heritage: I was born in India; came here to join my parents at 10 with no English language ability. With encouragement/support from my parents and teachers, I learned English, and I feel as if I have achieved my goals and dreams. I first learned of AAPI in medical school when I went to an AAPI meeting in CT. It was a great opportunity to meet individuals who looked like me and with similar beliefs or background; and who were successful-great role models for a young man like me.

I have always thought that the objective of AAPI is to bring out the best of physicians of Indian Heritage-whether it is via role models, philanthropic endeavors, social justice, medical teaching, etc. This has been crystallized with the formation of a peer reviewed medical journal-JAAPI. I wanted to support it and be a part of it. One night, I expressed my sincere interest in JAAPI. I was luckily accepted onto the Editorial Board. Initially, I had apprehensions about joining the group thinking it would be more like a social group; however, I was wrong. The group has been professional in all sense of the word. The group led by Dr. BK Kishore has adhered to one principle: excellence in everything. He has adapted the best practices from other journals, and he wants transparency in all aspects of the journal. He has educated the editorial board and welcomed opposing views and challenges---all to produce the best product. We have had some well respected and accomplished investigators/scientists who have come forward to contribute to the journal. The authors have been very receptive of the editorial board's comments and questions. The process represents the best of science---accept and answer to critiques. It is a beautiful process-I wish more of you could see this process in real time. I am happy and proud of this wonderful team. I encourage you to read the journal, offer comments and join. Thank you all for your wonderful support!

Suresh Karne, M.D., Ph.D.
Deputy Editor
Gastroenterologist

Indian Americans in the national spotlight have shone a light on the value of identifying proudly as a minority physician community with a voice. I am so honored to serve as a Deputy Editor for the JAAPI journal under the energetic leadership of Dr. Kishore. This journal provides a platform for good science and as the voice of the Indian American physician community, to develop the networks that buoy up newcomers and lift them up when they stumble. I can attest to the travails of being the only Indian American physician in a major academic University. However, striving for perfection has resulted in several colleagues achieving top-notch honors and recognition, while providing a roadmap to others who follow. I look forward to serving the community through sharing experiences and being part of this network to remind others that every ladder is worth climbing, every leadership position a feather in the collective community's cap!

Niharika Khanna, M.D., DGO
Deputy Editor
Family & Community Medicine

The JAAPI is a culmination of work started by many academically oriented members of AAPI, some successful and many failures. It is the will and the persistence of academically oriented members who saw the opportunity with the right environment and stepped forward to make the change. In addition, the journal has the potential to become the go-to journal addressing the health issues related to South Asians in America and the world. I would like to congratulate the AAPI leadership for supporting this effort wholeheartedly. I would like to thank Dr. BK Kishore who tirelessly resolved multiple issues and persisted with a single-track mind to get the journal embedded into the culture of AAPI.

I would like to encourage others to join in this effort to promote academic excellence and support the junior faculty, fellows, residents, medical students, and aspiring students who are fascinated by medicine and want to enhance their academic credentials. I can assure you, under the leadership of Dr. Kishore, structures have been put in place to keep the journal functional for a long time to come. I wish the entire team success and hope that they are able to keep the journal focused on academic pursuits and enhance the stature of our organization while contributing to science.

Vikas Khurana, M.D., MBA
Editorial Advisor
Gastroenterologist

I am honored to be affiliated with the groundbreaking academic initiative of the American Association of Physicians of Indian Origin (AAPI), The Journal of AAPI or JAAPI, as an Editorial Advisor. The Journal will contribute to the Excellence in Medical Research and Clinical Practices as a high-quality peer-reviewed publication. I look forward to the robust contributions of AAPI's talented Physicians to the growth and success of the Journal. This will be AAPI's legacy for future generations of Physicians. I sincerely congratulate the AAPI President Dr. Sudhakar Jonnalagadda for his vision of the Journal, Dr. Bellamkonda Kishore, for his energetic leadership as the Editor-in-Chief and Members of the JAAPI Editorial Board for their help and support.

Vemuri S. Murthy, M.D., M.S., FAHA, FICS
Editorial Advisor
Emergency Medicine

This Inaugural issue of JAAPI is the first fruit cultivated from a wonderful seed. The seed was an idea--the idea to foster academic and scientific publications in AAPI. With enthusiastic support from AAPI Executive Committee, including Dr. Suresh Reddy and Dr. Sudhakar Jonnalagadda, Dr. B. K. Kishore led the charge with diligence. I was fortunate to have been involved from planting the seed through the culmination of this first fruit. In the sapling stage, we meticulously edited and disseminated the Sushrutha Medical Newsletter on monthly basis. This set the tone and helped us engage the intellectual community as a successful transition to our ultimate goal: the launch of a peer-reviewed academic journal. There has been a lot of hard work, especially by our able leader, Dr. Kishore, leading to this point. It's exciting to reach the launch phase. This platform will provide an avenue to encourage and mentor the next generation of physicians, as well as improve the academic visibility of AAPI, and thus Indian Physicians. It has been a great honor to have been involved in such a great project from the beginning.

Soumya R. Neravetla, M.D., FACS
Deputy Editor
Cardiovascular & Thoracic Surgeon

It gives me immense pleasure to be a part of JAAPI, the first of its kind peer reviewed journal by Indian American Physicians. It has always been my dream to reach the pinnacle in medicine. Today, I am thankful for the whole JAAPI team and the Editor-in-Chief, Dr. B.K. Kishore for choosing me as a Deputy Editor of JAAPI and adding a feather in my cap. Teaching is my passion and I have been teaching junior physicians, residents, medical students and nurse practitioners for almost a decade. Evidence based practice has advanced the field of medicine. Peer-reviewed journals have been the main support resources to make clinical decisions. I am thrilled and happy to be a part of the JAAPI inaugural issue. From the Editorial Board selection to case review, it has been transparent process. The instructions of

selection process, case review, communication and peer reviewing guidelines have been spot on and crystal clear. I wish the best for our JAAPI team. I feel honored to be a part of this dedicated group of physician mentors who are the exponents and proponents of medical care. I know for sure that JAAPI will encourage medical aspirants, educate medical students, and nurse practitioners. It will also be a resource to guide residents and physicians when treating their patients. JAAPI will be an inspiration to all the Indian American physicians in their medical journey. Humble salutations and thank you all.

Pavan Kumar Panchavati
M.D., MPH, FHM, FAAP, SFHM
Deputy Editor
Hospitalist

About a year ago it was a vision of a handful of AAPI leaders to start a scientific publication for AAPI. This idea led to the development and publication of the extremely well-received Sushutra Medical News (SMN) – a monthly online newsletter full of medical articles and scientific narratives by AAPI members. After seeing the success of SMN amongst the community, this year under the leadership of AAPI President Dr. Sudhakar Jonalagadda, and SMN Editor-in-Chief Dr. BK Kishore, we are proudly launching the first peer-reviewed medical and healthcare journal of AAPI called Journal of the American Association of Physicians of Indian origin (JAAPI).

With this journal we hope to recognize the scientific research being done by AAPI members and other physicians worldwide. We intend to publish evidence-based studies, scientific narratives and peer-reviewed articles that highlight healthcare and medical topics. Several AAPI members are leaders in science, medicine, healthcare administration, healthcare policy, medical education and so much more. JAAPI will bring to the forefront the contributions of these leaders with a goal for all of us to elevate ourselves as a community with synergy.

I have been involved in the editorial boards and committees of SMN and now JAAPI from their inception. I have seen the hard work of Dr. Kishore in encouraging, inspiring and mentoring AAPI members including myself in thinking beyond our role as clinicians and using our creative energies towards bigger and better ideas to overall improvement of patient outcomes and healthcare in society. JAAPI will serve as that beacon of light within the AAPI community. AAPI is already known as an organization where Physicians of Indian origin can network, do charitable work, socialize, travel together, exchange ideas, etc. With JAAPI, a whole new dimension of adding scientific discussions will be brought to the AAPI community. I am excited to be part of this endeavor and am looking forward to this journey.

Kusum Punjabi, M.D., MBA, FACEP
Deputy Editor
Emergency Medicine

It gives me great pride and sense of accomplishment to be part of the team bringing out first issue of JAAPI, peer-reviewed journal of AAPI. Being the second largest organization of physicians in USA, lack of publication of peer-reviewed journal was a glaring deficiency for AAPI. With great enthusiasm and excitement, I hope long and overdue need for such a Journal will be fulfilled. I cannot emphasize enough the expertise of Dr. Kishore and support of Dr. Jonnalagadda in achieving this important milestone for AAPI. I sincerely hope the Journal provides much needed platform for budding academicians and seasoned practitioners.

Manoj Shah, M.D.
Deputy Editor
Pediatric Gastroenterologist

Acknowledgement

Birth of Peer-reviewed JAAPI during Pandemic

Bellamkonda K. Kishore, M.D., Ph.D., MBA

Editor-in-Chief of JAAPI

Correspondence: jaapi@aapiusa.org

COVID-19 pandemic has altered the way scientific and medical research is published and spread across the globe. Thanks to social media, the pandemic made RT-PCR, herd immunity, RNA and ACE2 etc. household names. AAPI pulsated, rose to the occasion, and initiated several projects in response to the pandemic. The pandemic has added another dimension to the educational outreach capability of AAPI in high-quality webinars by experts in the field. No doubt, the pandemic has brought out the best in AAPI, including the birth of JAAPI. As Freeman Dyson, FRS, aptly said *the pain of childbirth is not remembered, It's the child that's remembered*. To this I would like to add that the ordeal of the mother in carrying the baby for nine months in her womb is often ignored in the joy of celebrating the birth of a child. But, the joy of birth of JAAPI is clouded by the death of more than 580,000 Americans who succumbed to COVID-19, including about 3,000 healthcare providers, or the front line heroes in the United States alone. *We don't know them all, but we owe them all*. Our prayers are with the families of all those who have fallen to the pandemic.

That said, as the Editor-in-Chief, I fail in my duty if I do not acknowledge all those who participated in the birth of peer-reviewed JAAPI from its conception to delivery. A year ago, in its Governing Body Meeting in the Long Island, NY on February 8, 2020 AAPI announced its intention to launch a peer-reviewed medical and health journal. It was a joint decision made by Dr. Suresh Reddy, then President and Dr. Sudhakar Jonnalagadda, then President-Elect of AAPI. They entrusted the responsibility of preparing the groundwork for the birth of the journal to me. Following that, in association with Drs. Soumya Neravetla, Kusum Punjabi and Kavitha Das, Sushruta Medical News (SMN), a non-peer-reviewed medical and healthcare bulletin was started with monthly issues containing quality publications. With the success of SMN, we were prepared to launch JAAPI, the peer-reviewed Journal of the AAPI. In December 2020, an Ad hoc Editorial Advisory Committee of JAAPI was formed with me as the Chair, and Drs. Soumya R. Neravetla, Kusum Punjabi, and Kavitha Das as Co-Chairs, Drs. Ramasubbareddy Dhanireddy, Manoj Shah, Suresh Karne and Raj Alappan as Members, and Drs. Vemuri S. Murthy and Vikas Khurana as Editorial Advisors. The committee worked coherently with dedication and created an Editorial Board consisting of one Editor-in-Chief, 10 Deputy Editors, one Statistical Editor, 2 Editorial Advisors, and 10 Editorial Board Members. JAAPI is seeking more Deputy Editors and Editorial Board Members to cover various specialties. JAAPI also wants to recruit Editorial Interns (Medical Students, Residents, and Fellows) interested in gaining experience in editorial work.

Soon after formation of the Editorial Board, the Deputy Editors of JAAPI Drs. Raj Alappan, Sreenivas Chandana, Kavitha Das, Ramasubbareddy Dhanireddy, Suresh Karne, Niharika Khanna, Pavan Kumar Panchavati, Kusum Punjabi, and Soumya Neravetla, and the Editorial Advisors Drs. Vemuri Murthy and Vikas Khurana, actively sought articles for JAAPI, besides submitting their own articles. I would like to thank the entire team for their enthusiasm and dedication in the transformation of Sushruta Medical News into a peer-reviewed JAAPI. Their whole-hearted commitment has enabled this transformation smoothly. I thank all those who volunteered as Editorial Board Members. I also thank the authors who contributed to the inaugural issue of JAAPI with enthusiasm and thus supported our efforts.

I take this opportunity to thank all those who supported our efforts and encouraged us in publication of Sushruta Medical News, and in preparing the launchpad for JAAPI. Specifically, I would like to thank Drs. Suresh Reddy and Sudhakar Jonnalagadda for the initiative they have taken, the confidence they bestowed on us, and for their sustained and unconditional support during the past one year which made the birth of JAAPI possible today. I thank my co-editors of Sushruta Medical News, Drs. Soumya Neravetla, Kusum Punjabi and Kavitha Das, who worked hard in bringing out 11 monthly issues of SMN despite constraints imposed by the pandemic. I thank all authors who contributed to SMN. I thank the AAPI Executive Committee Members and Board of Trustees of 2020 and 2021. Last but not the least, thanks are due to Ms. Vijaya Kodali, Administrative Director for providing very efficient administrative support to SMN and JAAPI.

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Gastroenterology
Noble Medical Care, Upper Darby, PA

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University of Illinois College of Medicine, Chicago, IL

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Acquired Infections & Bacterial Infections
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Henry Ford Health System, Detroit, MI

Editorial Interns

This is for Medical Students and Residents.

Recruitment Criteria is in Preparation.

Scope of JAAPI

JAAPI is a peer-reviewed medical and health journal published by the AAPI. In line with the vision and mission of AAPI, JAAPI is dedicated to facilitate 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.

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 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. Based on type of the article, the length and specifications vary. 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 will be published as completely Open Access in electronic form (PDF). These will be archived in AAPI website, and the link to URL for each issue will be emailed to AAPI Members. 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: Soon after publication of the inaugural issue, JAAPI will obtain ISSN (International Standard Serial Number) for both electronic and print versions. After a year of publication, 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 will be added to ResearchGate, an European social networking site for scientists and researchers to share publications, discussions and collaborations. JAAPI will create a Twitter handle so physicians, healthcare professionals, academicians and scientists can follow the highlights of articles published in JAAPI.

Editorial Board: The Editorial Board of JAAPI consists of one Editor-in-Chief, several Deputy Editors covering different areas of medicine and health care, Statistical Editors, Editorial Board Members and Editorial Interns. In addition, there are Editorial Advisors to oversee long-term performance and stability of JAAPI and to help the Editorial Board Members in logistics, administrative and fiscal issues. The Editor-in-Chief and Deputy Editors are chosen based on their academic standing and/or professional experience in editing and reviewing manuscripts for journals. The Deputy Editors will handle the review process of submitted papers helped by internal (Editorial Board Members) and external reviewers. Editorial Interns are medical students or residents who would like to obtain training in editing for journals. They will work with the Deputy Editors. AAPI membership is required for all Editorial Board Members, who are expected to promote the vision and mission of AAPI through JAAPI.

CME Credits for Peer-Review Process: After indexing by PubMed, working through AAPI, JAAPI will obtain CME Credit eligibility for its reviewers by the Accreditation Council for Continuing Medical Education of the American Medical Association. Several journals are offering CME credits to their reviewers.

Journal Periodicity: Initially, JAAPI will have three issues per year (Spring, Summer, and Fall). As the journal picks up momentum and article submissions increase, the periodicity will be quarterly or even more frequent.

Types of Articles JAAPI Accepts:

- **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 up to 3,500 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 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 up to 3,000 to 4,000 words, excluding title page, abstract, references, and legends. Not over 5 figures and tables combined. There is no limit on the number of references, but they should be recent and relevant ones.
- **Clinical Studies:** Clinical studies can be observational or retrospective analysis of data or prospective randomized studies. All clinical studies should be conducted under the regulations and guidelines, documenting informed consent, protection of research subjects, inclusion of minorities etc., as per the guidelines of the US Public Health Service. Rigorous statistical analysis should be followed. Raw data should be provided for analysis if required. These articles can be up to 3,000 words, excluding title page, abstract, tables, legends, and references. Maximum number of figures or tables are 7 combined. Additional figures or tables should be justifiable for the study. Supplemental Information (SI) is allowed for deposition.
- **Brief Reports:** Brief reports of contemporary issues of high significance are accepted to disseminate information. These reports are up to 1,500 words in length, excluding title page, abstract, legends and references. About 4 tables or figures combined are permitted. Maximum 15 references are allowed.
- **Letters to the Editor:** Letters to the editors on topics of high importance or on the articles published in JAAPI are welcome. These should be focused and carry significant take home message, rather than a simple presentation of one's own perspective on the topic. These can be up to 600 words in length with 6 references, 2 small tables or figures maximum. The authorship should be limited to 2 or 3. No abstracts are allowed.
- **Articles on Diagnosis and Treatment Review:** Article describing latest methods, approaches and technologies in diagnosis and treatment can be up to 2,000 words, excluding title page, abstract, references, and legends. Figures and tables should be limited to five combined.
- **Case Studies or Clinical Challenges:** Case presentation with about 300 to 400 words, followed by discussion of 500-600 words, 1-2 small figures, and less than 10 references, are welcome. The authorship should be limited to 3 unless it involves trainees. Proof of patient consent should be provided.
- **Perspectives on Contemporary or Controversial Topics:** These should be thought-provoking with intuitive analysis rather than presentation of facts. Some speculation and hypothesis is permitted provided they are supported by rational analytical base. These articles can be up to 1,200 words, excluding title page, abstract, legends and references. Less than 3 tables or figures combined are allowed. References should be limited to the required ones.

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- **Commentaries on Published Papers:** Commentaries on published papers are accepted if they provide a different post-publication perspective not explicit or missed in the original publications. These can either positively or negatively affect the original publication. But the emphasis is how the original publication can affect clinical practice or evidence-based medicine. These can be 600-800 words in length with one or two figures or tables, and limited references. No abstract is allowed. Authorship should be limited to one or two.
- **Bench-to-Bedside or Bedside-to-Bench:** Authors can take laboratory findings to clinical settings or bring clinical dilemmas to laboratory research. Special emphasis should be made on moving the subject from bench to bedside or vice versa. This type of articles can be up to 1,200 words in length, excluding title page, abstract, legends and references. Not over 3 tables or figures combined are allowed. References should be limited to the required ones.

References Style: JAAPI follows the same style as JAMA for presentation of references, which can be found in the following URL. <https://www.bibguru.com/c/jama-citation-generator/>

Disclosures: All authors should disclose industry relations, including speaker's bureau, research grants, travel funds, stocks over \$10,000 owned by them or their immediate family members, etc., which can be construed as conflicting with the content of the article being submitted. When in doubt whether a particular industry relation is a conflict, the authors should consult the editorial office.

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Proprietary Names: While citing names of drugs or medications, authors should avoid brand names and use generic or pharmacological names only.

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Contact Information: A dedicated portal for JAAPI will be created in AAPI website soon. Until that time, for further information about JAAPI or to submit articles, please email to jaapi@aapiusa.org. One can also directly contact the Editor-in-Chief or any Deputy Editor, who will respond to your questions.

JAAPI is Seeking Deputy Editors & Editorial Board Members.

General Criteria for Recruitment of Editorial Board Members: Since JAAPI represents the interests of AAPI, prospective Editorial Board Members should be Patron Members of AAPI and should subscribe to the vision, mission and core values of AAPI, and thus promote them in letter and spirit. In case, the prospective Editorial Board Member is not a member of AAPI, he/she should be willing to become a member and subscribe to the vision, mission, and core values of AAPI and promote them. The Editorial Board works with team spirit, collegiality and mutual understanding and respect. Hence it calls for coherence, comradeship, and synergy in work in the best interest of AAPI. It also needs good interpersonal and communication skills. In this respect, working on the Editorial Board of JAAPI is not the same as working on the Editorial Board of other journals, where members can work in isolation and not as a community.

Deputy Editors: Deputy Editors take responsibility for the review process of articles from submission until the final decision about their suitability for publication. They work with expert reviewers in their specialty, get the review work done, and submit their recommendations to the Editor-in-Chief. Thus, Deputy Editorship involves serious time commitment, ability to work independently, and take decisions during review process. Ideally, the candidates should have considerable experience in writing, publications, and reviewing papers as well as editorial experience. Affiliation with an academic institute or Veterans Affairs Medical Center or federal agencies, such as Food and Drug Administration (FDA) or Centers for Disease Control and Prevention (CDC) are preferred. The specialties under consideration for Deputy Editors are Anesthesia and Pain Management; Cardiology; Endocrinology and Metabolic Diseases; Geriatric and Palliative Medicine; Immunology & Rheumatology; Allergy & Infectious Diseases; Obstetrics and Gynecology; Ophthalmology; Orthopedics and Sports Medicine; Ear, Nose and Throat Diseases; Neurology; Pulmonary Medicine; Surgical Specialties (except Cardiovascular Surgery); Transplantation Medicine; Radiology and Imaging.

Editorial Board Members: JAAPI is also seeking to recruit Editorial Board Members to review submitted articles in various specialties. Editorial Board Member review manuscript in their specialties assigned to them by the Deputy Editors. Similar to the Deputy Editors, prospective Editorial Board Members need to be Patron Members of AAPI or should become members before taking up their role in the Editorial Board. They need to subscribe to the vision, mission, and core values of AAPI and support them. Ideally, the Editorial Board Members should have experience in publication and reviewing journal articles. Affiliation with academic institutes or Veterans Affairs Medical Center or a federal agency, such as FDA or CDC is a plus. They should be willing to commit time to complete the review process on a timely fashion. Editorial Board Members are needed in the following specialties: Anesthesia and Pain Management; Endocrinology and Metabolic Diseases; Emergency Medicine and Critical Care; Epidemiology and Public Health; Immunology and Rheumatology; Allergy and Infectious Diseases; Obstetrics and Gynecology; Ophthalmology; Orthopedics and Sports Medicine; Neurology; Transplantation Medicine; and all Surgical Specialties.

Editorial Interns: Editorial Internship is for Medical Students and Residents interested in gaining mentored training in editorial process. The criteria and guidelines for selection are under preparation and will be published soon.

Applications and Review Process: Prospective applicants are requested to send their updated curriculum vitae along with a note of their interests to the Editor-in-Chief by emailing to jaapi@aapiusa.org. All applications will receive full review and evaluation by the Editor-in-Chief and the Deputy Editor. Decisions are made by merit and consensus or voting.

In-depth Review

From Heart to Brain: Occult Atrial Fibrillation, Atrial Cardiopathy, and Stroke

Mitchell S.V. Elkind, M.D., M.S.^{1,2}

¹Department of Neurology, Vagelos College of Physicians and Surgeons;

²Department of Epidemiology, Mailman School of Public Health;
Columbia University, New York, NY, USA

Edited by:
Soumya R. Neravetla, M.D.

Reviewed by:
Gunjan J. Shukla, M.D.
New York Medical College,
New York, NY

Anil V. Yallapragada, M.D.
VA Palo Alto Health Care System,
Palo Alto, CA

Correspondence:
mse13@columbia.edu

Received: February 2, 2021

Accepted: April 10, 2021

Citation:
Elkind MSV, JAAPI 1(1):21-30, 2021

Abstract: Atrial fibrillation (AF) is a well-known cause of stroke, and the only common stroke mechanism for which anticoagulation has been demonstrated to be beneficial. Because AF may occur infrequently and in short bursts, however, it may be hard to diagnose in patients with stroke, and recent evidence has suggested that prolonged rhythm monitoring may be of value in patients with unexplained stroke to capture episodes of paroxysmal AF that warrant anticoagulation. Recent evidence suggests that an abnormal left atrial substrate, even in the absence of AF, may serve as a risk factor for stroke. The term atrial cardiopathy may describe this condition in those patients at increased risk of stroke due to atrial dysfunction in the absence of known frank AF. Biomarkers of left atrial dysfunction may detect atrial cardiopathy. Federally funded clinical trials are now testing the hypothesis that anticoagulant treatment of patients with atrial cardiopathy will reduce the risk of recurrent stroke.

Key Words: Atrial Cardiopathy; Atrial Disease; Atrial Fibrillation; Cardioembolic Stroke; Cerebrovascular Disease; Stroke Prevention

Introduction: Atrial fibrillation (AF) is a long-recognized cause of stroke; its significance lies in being the only common stroke mechanism for which anticoagulation has been of benefit. Recently, however, there have been several further advances in our understanding of the relationship of AF to stroke. First, the search for short, infrequent episodes of paroxysmal AF — what we might call “occult AF” -- has become increasingly relevant to the management of patients with ischemic stroke. Second, recent evidence suggests that patients with biomarkers of left atrial dysfunction without a history of frank AF—what we have labeled “atrial cardiopathy”—are also at increased risk of stroke (1). Third, clinical trials are testing the hypothesis that anticoagulant treatment of patients with atrial cardiopathy may reduce the risk of recurrent stroke, just as they do those with AF. If confirmed, this may also open the door to trials of anticoagulants for primary stroke prevention in those with atrial cardiopathy.

Unexplained Stroke and Occult Atrial Fibrillation: Approximately a third of ischemic strokes are considered unexplained after thorough evaluation (2). Initially, strokes of unknown cause were referred to as “cryptogenic”, indicating the mystery of their origins. The definition of cryptogenic stroke permitted inclusion of patients in whom a full evaluation had not been conducted. Today, the term “embolic stroke of undetermined source”, or ESUS, is used to reflect the common understanding these strokes often have a cardiac origin, albeit from a less well-established cardiac source (3). The advantage of the ESUS concept is that it requires the stroke patient undergo a full etiologic evaluation, including the exclusion of (i) small, deep infarcts in the distribution of penetrating cerebral vessels; (ii) intracranial or extracranial stenosis through vascular imaging; (iii) a definite cardioembolic source through transthoracic echocardiography, electrocardiography, and at least 24 hours of cardiac monitoring; and (iv) other well-defined unusual causes of stroke such as

vasculitis, hypercoagulability, or dissection. These infarcts, which usually affect the territory of major branches or

distal end vessels of cerebral arterial system, suggest a remote embolic source (Figure 1).

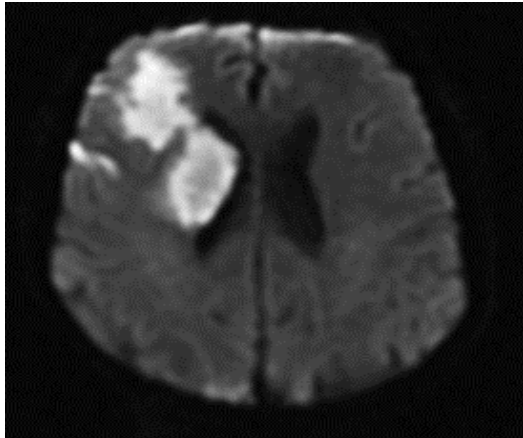


Figure 1. Diffusion-weighted Magnetic Resonance Imaging scan of the brain in a 78 year old man with a history of hypertension and rheumatoid arthritis who presented with acute confusion. He was initially evaluated as an outpatient, and was referred for this scan. He was subsequently found on examination to have a mild left hemiparesis. The scan shows infarction in both superficial and deep territories of the right middle cerebral artery, consistent with embolism to this artery. No etiology of the stroke could be found on initial evaluation, but several months later he was found to have brief runs of atrial fibrillation using an implanted cardiac monitor.

Table 1. Biomarkers Associated with Atrial Cardiopathy and Stroke Risk

Category of Biomarker	Specific Examples
Atrial Fibrillation	Permanent atrial fibrillation Paroxysmal atrial fibrillation "Occult" (Difficult to diagnose, infrequent intermittent paroxysmal atrial fibrillation)
Atrial Ectopy	Excessive supraventricular ectopic activity Paroxysmal Supraventricular Tachycardia Prolonged PR interval Increase P-wave Terminal Force in lead V1 (PTFV1)
Atrial Structural Abnormalities	Left atrial enlargement Left atrial appendage morphological variations Myocardial fibrosis
Atrial Functional Abnormalities	Reduced left atrial appendage flow velocity
Serum Biomarkers	N-terminal pro B-type natriuretic peptide (NT-proBNP) High-sensitivity cardiac troponin T (cTnT)
Measures of Thrombotic Potential	Spontaneous echocardiographic contrast
Genetics	Genes associated with atrial fibrillation

Source: Elkind MSV, Practical Neurology, January 2020, pp 38-41

Occult paroxysmal AF (PAF) is one potential mechanism of ESUS. It is essential to find PAF in ischemic stroke patients because oral anticoagulants substantially reduce the risk of stroke, and stroke recurrence, in patients with AF (4, 5). Because AF may be asymptomatic, intermittent, and infrequent, however, many patients do not have a history of AF or electrocardiographic evidence during the often brief hospital stay during stroke. As many as 25% of patients with AF do not know they have the disorder until a thromboembolic event occurs (6).

Similarly, history alone is generally not helpful in suggesting a diagnosis of AF, since most patients with palpitations or tachycardia are in sinus rhythm or other types of benign dysrhythmia when these symptoms occur. Thus, additional cardiac monitoring is now usually employed to detect AF after unexplained strokes.

Randomized controlled trial evidence demonstrated that outpatient cardiac monitoring after ESUS increases the rate of detection of AF beyond that

accomplished with the guideline-recommended standard 24-hour monitoring approach. The 30-Day cardiac Event Monitor Belt for Recording paroxysmal Atrial fibrillation after a Cerebral ischemic Event (EMBRACE) trial showed that 30 days of continuous monitoring with an external device was superior to 24 hours of continuous monitoring (7). The CRYptogenic STroke And underLYing Atrial Fibrillation (CRYSTAL-AF) trial demonstrated the benefit of using an implanted cardiac monitoring device that can capture PAF for up to 3 years after implantation, compared to standard monitoring (8). These trials shared as their primary outcome the detection of AF, rather than clinical outcome events such as stroke. Thus, although they showed an increase in AF detection, they did not prove a reduction in clinical events, and therefore clinical guidelines do not endorse long-term cardiac monitoring in the strongest terms. But the trials did provide evidence that detection of AF had clinical implications. For example, over 95% of patients with AF detected were placed on oral anticoagulation therapy for secondary stroke prevention. In CRYSTAL-AF, the 1-year stroke rate was reduced among those randomly assigned to the implanted monitor compared to patients assigned to conventional monitoring, though the result did not reach statistical significance (7.1% vs. 9.1%, $p > 0.05$). Because studies have not yet compared 30 days of monitoring to a longer time window, such as three years, the duration of monitoring remains uncertain. The secondary prevention guidelines recommend consideration of 30 days of cardiac monitoring (9), but they fall short of making a stronger recommendation.

In practice it is likely that decisions about how long to monitor patients will depend on patient characteristics. The search may include Holter monitoring for 24 to 72 hours, a two- to four-week external cardiac monitor, or an implanted cardiac monitor that can be worn for 3 years or longer. The likelihood of detecting AF can be predicted by patient history and electrocardiographic indices, like a prolonged PR interval (10) or biomarkers, like Brain Natriuretic Peptide (11). Sometimes, a shorter period of monitoring may disclose subtle abnormalities short of AF that warrant further study with longer-term monitoring. As an example, one elderly woman with a small stroke had frequent ectopy on an initial external monitor, but this fell short of AF. We continued monitoring her longer with an external device, and she then manifested frank AF, at which

point anticoagulation was initiated (12). Anecdotally, we have also been surprised by the number of patients who indicate a preference for an implanted device rather than an external monitor, and we have further found that implanted devices are often better accepted by acute rehabilitation facilities after stroke, as they do not require active management by nursing staff.

Atrial Cardiopathy in Patients with Atrial Fibrillation:

The mechanism of embolic stroke in patients with AF is usually thought to be due to “Virchow’s triad” establishing the conditions for thrombus formation: stasis, coagulability, and endothelial injury or dysfunction. Many of us learned in medical training that the fibrillation of the atrium—imagine the classic appearance of the atrium as a “bag of worms” due to its wriggling walls—straightforwardly explains how AF leads to embolic stroke. The lack of effective atrial contraction leads to stasis, permitting blood clots to form in the left atrium or the left atrial appendage (LAA); those clots can then embolize to the brain or systemic circulation. In this model, stasis in the fibrillating atrium creates the risk of stroke.

Recent evidence, however, suggests the picture may not be so simple (Scheme 1). There is evidence that very brief, asymptomatic runs of PAF occur commonly and that even brief, asymptomatic runs of AF may be associated with an increased risk of ischemic stroke. There is also a temporal disassociation between when patients with paroxysmal AF are fibrillating and when the embolic stroke occurs. Patients with PAF may suffer ischemic strokes even when they are not in AF, even weeks removed from their AF. In the ASSERT and TRENDS studies, among patients with implanted cardiac devices that could assess rhythm, only 8-28% of patients were in AF in the 30 days before their stroke (13, 14). Because epidemiological logic dictates that a clear temporal association is critical to ascribing causality to a risk factor, the absence of a consistent temporal association between AF and stroke suggests that a fibrillating atrium itself may not be the proximate cause of stroke in many patients with AF.

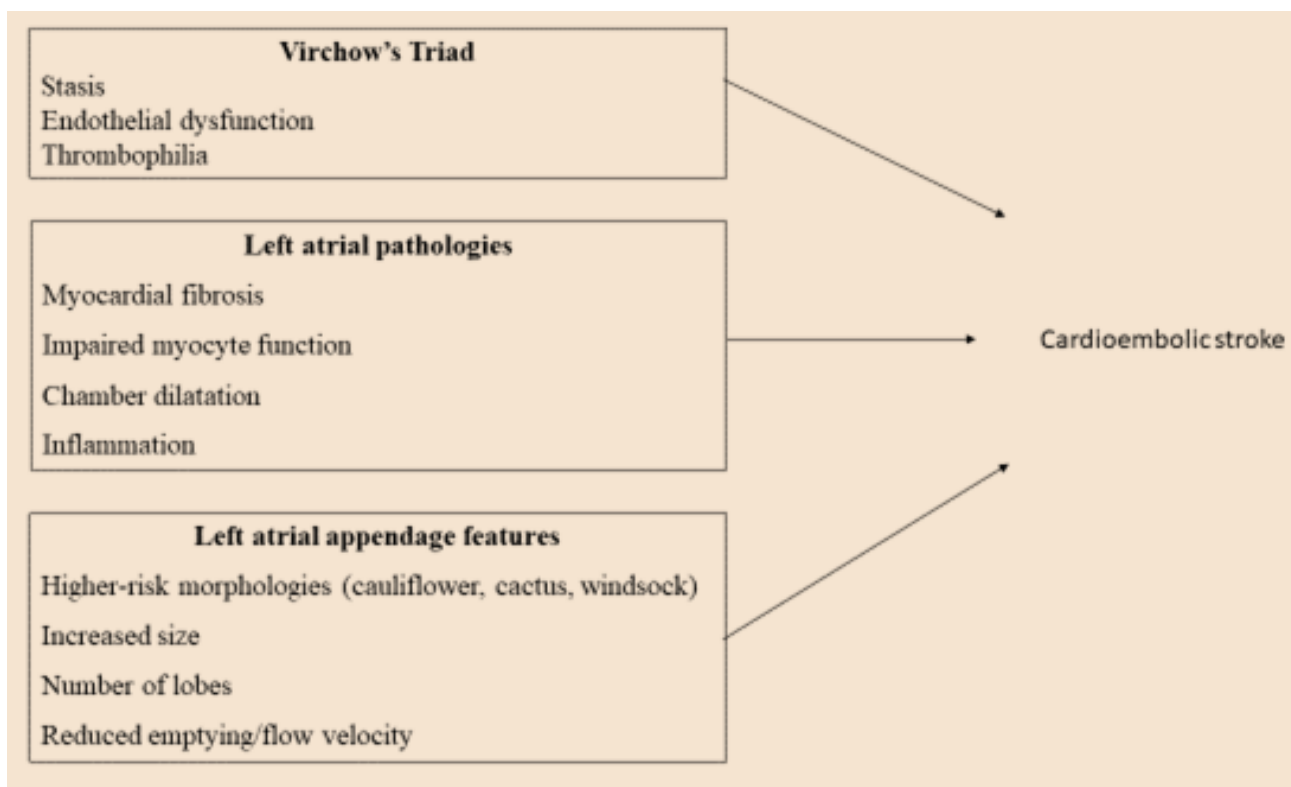
There are additional lines of evidence suggesting that it is the underlying abnormal atrium, and not the fibrillation *per se*, that contributes to stroke risk. We have argued AF may be a marker of stroke risk, rather than its direct cause (15). Cardiac conduction abnormalities other than AF, such as paroxysmal supraventricular tachycardia

and excessive supraventricular ectopic activity, for example, are associated with doubling stroke risk, even in the absence of known AF (16). Echocardiographic evidence of atrial contraction and flow patterns typical of AF may also occur despite apparent electrical normal sinus rhythm seen on the surface ECG (17). Genetic polymorphism associated with AF may also contribute to stroke even before patients develop evidence of AF by ECG (18).

The most common site for thrombus formation is the LAA, rather than the fibrillating atrium itself. Thrombi are present in the LAA in over 90% of AF patients (19). The LAA may have different morphologies, which are often

described using colorful and evocative terminology: chicken wing, cactus, windsock, and cauliflower. These shapes and configurations appear to correlate with embolic potential in patients with AF. Among 932 AF patients, for example, the cactus, windsock, and cauliflower LAA morphologies were associated with a higher stroke risk than chicken wing morphology (20). It is plausible that the increased trabeculations and lobules found in those AF patients with LAA morphologies other than the more common chicken-wing shape contribute to the likelihood of thrombus formation (19).

Scheme 1: Mechanisms of Atrial Disease Leading to Cardioembolic Stroke



Other types of acquired abnormalities of the left atrium may also potentially provide a ground for thrombus formation by promoting stasis, endothelial dysfunction, and hypercoagulability (17, 21). For example, left atrial enlargement (LAE) was associated with spontaneous echocardiographic contrast, which is considered as an echocardiographic marker of a prothrombotic tendency, and frank thrombus formation. Developing endothelial

dysfunction and hypercoagulability may also occur in diseased atria before onset of stasis or frank AF. Accumulation of fibrotic tissue over time within the myocardium is also an important cause of AF, which may increase risk of cardiac embolism independent of AF (22). Atrial fibrosis may precede AF or be present even in the absence of development of AF.

Table 2. Selected Recommendations from Recent Guidelines Related to Atrial Fibrillation and Stroke Risk

Class of Recommendation	Level of Evidence	Recommendation	Reference
I	A (warfarin) B (dabigatran) B (rivaroxaban) B (apixaban) B-R (edoxaban)	For patients with AF and an elevated CHA ₂ DS ₂ -VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban.	January et al, 2019 Ref # 34
I	A	Direct-acting oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).	January et al, 2019 Ref # 34
I	B	In patients with AF (except with moderate to-severe mitral stenosis or a mechanical heart valve), the CHA ₂ DS ₂ -VASc score is recommended for assessment of stroke risk.	January et al, 2019 Ref # Error! Bookmark not defined. 34
I	B	Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.	January et al, 2019 Ref # 34
I	C	In patients with AF, anticoagulant therapy should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences.	January et al, 2019 Ref # 34
I	C	For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF.	January et al, 2019 Ref # 31
Ila	B-R	In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF.	January et al, 2019 Ref # 34
Ila	C	For patients who have experienced an acute stroke or TIA with no apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within 6 months of the index event.	Kernan et al, 2014 Ref # 35

Footnote to Table 2: Class of recommendation refers to the strength of the recommendation. Class I recommendations are regarded as strong (recommended), in which the benefit greatly outweighs the risk. **Ila** is regarded as moderate (reasonable), in which benefit somewhat outweighs risk. Level of evidence is categorized by the strength of the supporting evidence for the recommendation. **A** refers to evidence from 1 or more high-quality randomized controlled trials (RCTs) or meta-analyses from high quality RCTs. **B** refers to evidence from at least 1 RCT or meta-analyses of moderate quality RCTs; **R** refers to a randomized trial; category **B** may also include non-randomized studies. **C** refers to more limited data, including observational or registry data, meta-analyses, physiological studies, or expert opinion. Further details about these classifications and the recommendations themselves are provided in the references.

These data suggest that the appearance of AF on an electrocardiogram may not be the sole mechanism of embolic events in patients with evidence of atrial

dysfunction (1). The electrocardiographic hallmark of AF may simply be another biomarker of an underlying risk of embolic stroke associated with atrial dysfunction, rather

than a proximate cause. Other mechanisms, such as other supraventricular arrhythmias, genetic factors, atrial enlargement, fibrosis, inflammation, and coagulation disturbances in patients with an underlying abnormal atrial substrate, may account for embolic stroke even without AF being present. Thus, the classic notion of a fibrillating atrium serving as a “bag of worms” and leading to stroke may require revision.

Atrial Cardiopathy and Stroke: Currently, however, there is no consensus on how atrial cardiopathy should be defined. It is not even formally accepted as a disease. Left atrial dysfunction occurs along a continuum progressing from normal to severe condition. Along this continuum, the risk of thromboembolic events increases. There are potential biomarkers indicative of atrial cardiopathy, however, including structural, electrophysiological, imaging, and serum biomarkers (Table 1).

Population-based studies revealed that left atrial enlargement (LAE) is associated with incident ischemic stroke risk, even after adjusting for several confounders, including AF. In the Northern Manhattan (n = 655 patients, median follow up 4 years), moderate to severe LAE independently predicted stroke recurrence, and in particular predicted likely embolic strokes (adjusted HR 2.83, 95% CI 1.03-7.81) (23).

P-wave terminal force in lead V1 (PTFV1) on a standard ECG reflects electrical conduction through the atria. PTFV1 is a marker of atrial dysfunction and risk of ischemic stroke. Studies have shown that increased PTFV1 predicts incident AF and ischemic stroke risk independently of AF. In the Northern Manhattan Study, PTFV1 predicted incident ischemic stroke (adjusted HR 1.20, 95% CI 1.03-1.39) and particularly stroke of embolic subtypes (adjusted HR 1.31, 95% CI 1.08-1.58) (24). Electrocardiographic PR interval prolongation ≥ 200 ms is another possible electrocardiographic biomarker of atrial disease (25).

Serum biomarkers indicative of cardiac dysfunction, and particularly of atrial dysfunction, have been associated with stroke risk, even in patients without known atrial fibrillation (Table 1). N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP), for instance, released by the myocardium in response to stretch, increases in heart failure, structural heart disease, AF, and other situations of ventricular strain (26). Concentrations of NT-proBNP predict cardiovascular events, including incident AF, detection of AF after stroke, subclinical cerebrovascular disease, and cardioembolic stroke (27), though further

research is needed to determine causal mechanisms rather than associations.

There are several other potential biomarkers of atrial cardiomyopathy, including atrial fibrosis, atrial strain, and atrial ejection fraction, that have been explored in several studies. For example, late gadolinium enhancement on cardiac magnetic resonance imaging can detect atrial fibrosis, and has been associated with incident atrial fibrillation detected by long-term monitoring (28). In a study among 387 patients (n=36, or 9.3% with prior stroke), there was a higher proportion of atrial fibrosis among those with stroke and those with higher CHADS₂ scores (29). In a European study among 400 healthy participants (and without AF) who underwent two-dimensional speckle tracking echocardiography of the left atrium followed for a median of 16 years, peak atrial longitudinal strain predicted AF in participants aged <65 years but not older, after adjusting for comorbidities; atrial strain also predicted a composite outcome of AF and stroke, significant after multivariable adjustment (30). Left atrial strain has also been associated with subclinical infarcts detected on MRI in the multiethnic Northern Manhattan Study population (31). In the same population, left atrial volumes and left atrial ejection fraction were associated with subcortical infarcts and white matter disease, suggesting that both cardioembolism and reduced perfusion may contribute to cerebrovascular injury in those with atrial cardiopathy, though more research is needed (32).

Only a few studies have simultaneously explored multiple biomarkers of atrial cardiopathy in relation to stroke risk. In the Cardiovascular Health Study, among 3,723 participants free of both stroke and AF at baseline, PTFV1 (HR per 1,000 $\mu\text{V}\cdot\text{ms}$ 1.04; 95% CI 1.001-1.08), NT-proBNP (HR per doubling of NT-proBNP 1.09; 95% CI 1.03-1.16), and incident AF (HR 2.04; 95% CI, 1.67-2.48) were each independently associated with incident stroke. Left atrial dimension was not associated with stroke risk independently of these other markers (33). These findings suggest that electrocardiographic and serum biomarkers may be early correlates of atrial cardiopathy, occurring even before structural changes in the atrium.

Clinical Implications: Selected recommendations from recent guidelines on anticoagulant management for stroke prevention in patients with discovered AF, and recommendations for testing for AF in patients with unexplained stroke, are summarized in Table 2 (34, 35).

Patients with atrial cardiopathy, even without evidence of AF, may benefit from treatment with anticoagulants to prevent recurrent stroke, just as patients with AF do. Among patients in the Warfarin Aspirin Recurrent Stroke Study (WARSS), a multicenter randomized trial of anticoagulation with warfarin versus aspirin in the secondary prevention of stroke among patients with strokes of non-cardioembolic mechanism, there was evidence of reduced risk of stroke or death among those with elevations in NT-

proBNP. Among patients with NT-proBNP >750 pg/ml, treatment with warfarin was associated with a reduced risk of stroke or death at 2 years when compared to treatment with aspirin (P=0.021).

Table 3. Selected Major Inclusion and Exclusion Criteria for the ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke) Trial

Inclusion Criteria

- Age ≥45 years.
- Clinical diagnosis of ischemic stroke and brain imaging to rule out hemorrhagic stroke.
- Modified Rankin Scale score ≤4.
- Ability to be randomized no later than 180 days after stroke onset.
- Embolic Stroke of Undetermined Source, defined as all of the following (1):
 - Stroke that is not lacunar. Lacunar is defined as a subcortical (this includes pons and midbrain) infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension is ≤1.5 cm on CT, ≤2.0 cm on MRI diffusion images, or ≤1.5 cm on MRI T2-weighted images. The following are not considered lacunes: multiple simultaneous small deep infarcts, lateral medullary infarcts, and cerebellar infarcts. Patients with a clinical lacunar stroke syndrome and no infarct on imaging are excluded.
 - Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis of the artery supplying the area of ischemia. Patients must undergo vascular imaging of the extracranial and intracranial vessels using either catheter angiography, CT angiogram (CTA), MR angiogram (MRA), or ultrasound, as considered appropriate by the treating physician and local principal investigator.
 - No major-risk cardioembolic source of embolism, including AF, intracardiac thrombus, mechanical prosthetic cardiac valve, atrial myxoma or other cardiac tumors, moderate or severe mitral stenosis, myocardial infarction within the last 4 weeks, left ventricular ejection fraction <30%, valvular vegetations, or infective endocarditis.
 - No other specific cause of stroke identified, such as arteritis, dissection, migraine, vasospasm, drug abuse, or hypercoagulability.

Exclusion Criteria

- History of atrial fibrillation, atrial fibrillation on 12-lead ECG, or any atrial fibrillation of any duration during heart-rhythm monitoring prior to randomization.
- Clear indication for treatment-dose anticoagulant therapy, such as venous thromboembolism or a mechanical heart valve.
- Left ventricular ejection fraction <30%.
- Definite indication for antiplatelet agent
- History of spontaneous intracranial hemorrhage
- Chronic kidney disease with serum creatinine ≥2.5 mg/dL.
- Active hepatitis or hepatic insufficiency
- Clinically significant bleeding diathesis
- Chronic anemia (hemoglobin <9 g/dL) or thrombocytopenia (<100 x 10⁹/L)
- Clinically significant gastrointestinal bleeding within the past year
- Pregnancy or risk of pregnancy
- Known allergy or intolerance to aspirin or apixaban.

Source: Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA)
<https://clinicaltrials.gov/ct2/show/NCT03192215>

Similarly, in a secondary analysis of the NAVIGATE-ESUS trial (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Source), there was evidence that anticoagulation was of benefit greater than aspirin among patients with moderate to severe left atrial enlargement (36). These results, albeit from secondary analyses, provide a rationale for a clinical trial to test anticoagulation against the standard of care antiplatelet therapy among patients with ESUS and atrial cardiopathy (37).

We are conducting such a trial, ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke trial; clinicaltrials.gov NCT03192215), supported by the National Institute of Neurological Disorders and Stroke (NINDS) (38). The trial will test the hypothesis that the direct acting oral anticoagulant apixaban is superior to aspirin to prevent recurrent stroke in patients with ESUS and atrial cardiopathy, but without known AF. The secondary objective of the trial is to test the hypothesis that the relative efficacy of apixaban over aspirin increases with the severity of atrial cardiopathy. The trial is being conducted through the NINDS StrokeNet mechanism, and is also supported by the Bristol Meyers Squibb-Pfizer Alliance for Eliquis® and Roche. ARCADIA will randomly assign 1100 patients with ESUS and atrial cardiopathy to either apixaban 5 mg twice daily (or a dose of 2.5 mg twice daily to those who meet criteria for a reduced dose) or to aspirin 81 mg daily (Table 3). All patients must have standard diagnostic testing to exclude small vessel strokes, large artery stenosis, and definite source of cardioembolism, including AF. Then, in a second step before randomization, participants undergo testing for one of three biomarkers of atrial cardiopathy:

- PTFV₁ >5,000 μ V*ms on 12-lead ECG;
- Serum NT-proBNP >250 pg/mL;
- Left atrial diameter index ≥ 3 cm/m² on echocardiogram (severe left atrial enlargement).

The primary efficacy endpoint of ARCADIA is recurrent stroke of any type (ischemic, hemorrhagic, or of undetermined type). The secondary efficacy endpoints are: (a) composite of recurrent ischemic stroke or systemic embolism, and (b) composite of recurrent stroke of any type or death from any cause. Safety will also be assessed.

Although the level of each biomarker most appropriate for determining atrial cardiopathy remains uncertain, using several biomarkers, relatively low thresholds, and the requirement that only one criterion be

met should facilitate testing of the secondary ARCADIA hypothesis that atrial cardiopathy represents a spectrum of illness, with different levels of severity. Ideally, this will provide clinicians with the information needed to balance the risks and benefits of anticoagulation in patients with atrial cardiopathy.

Conclusion: Occult AF is an important risk factor for stroke, and cardiac rhythm monitoring in patients with unexplained stroke is of great value to detect AF. In addition, atrial cardiopathy may constitute one mechanism of unexplained stroke, and patients with evidence of atrial cardiopathy constitute a group of patients in whom clinical trials are warranted to test anticoagulation versus antiplatelet therapy to reduce stroke recurrence risk. Further studies are warranted to (i) determine overlap among atrial cardiopathy biomarkers, and (ii) establish which biomarker(s), alone or in combination, is(are) most useful in predicting the risk of stroke and response to anticoagulation therapy.

Disclosure: Dr. Elkind receives royalties from UpToDate® for a chapter on cryptogenic stroke. He also receives research support in kind from the BMS-Pfizer Alliance for Eliquis®; receives research support from Roche; and serves as an Officer of the American Heart Association/ American Stroke Association.

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State-of-the-Art Review

Endoscopic Management of Achalasia Cardia: An Update

Zaheer Nabi, M.D., DNB, and D. Nageshwar Reddy, M.D., DM

Asian Institute of Gastroenterology, Hyderabad 500 082, India

Edited by:

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

Pavan K. Panchavati, M.D., MPH

Reviewed by:

Ram Hawari, M.D.

*Digestive Center-Huntsville
Hospital, Huntsville, AL*

Correspondence:

Zaheer Nabi

zaheernabi1978@gmail.com

D. Nageshwar Reddy

aigindia@yahoo.co.in

Received: January 28, 2021

Accepted: March 17, 2021

Citation:

Nabi Z, Reddy DN,

JAAPI 1(1): 31-41, 2021

Abstract: Achalasia cardia is characterized by absence of esophageal peristalsis in conjunction with incomplete relaxation of lower esophageal sphincter (LES). Achalasia is diagnosed by endoscopy, barium swallow and high-resolution manometry in cases with compatible symptoms. The endoscopic management of achalasia includes botulinum toxin injection, pneumatic dilatation and per-oral endoscopic myotomy (POEM). Of these, botulinum injection is the least durable modality and usually reserved for elderly and frail patients unsuitable for other treatment options. Graded pneumatic dilatation is a relatively durable treatment option and recommended for suitable patients with type I and II achalasia. Young age (<40 years) and type III achalasia are the most important negative predictors for response with pneumatic dilatation. Therefore, these cases should be preferably managed with POEM or laparoscopic Heller's myotomy. POEM is a novel endoscopic treatment modality for achalasia. The safety and short-term efficacy of POEM is well-established and the major societal guidelines have incorporated it into the management algorithm for achalasia. The main advantage of POEM over Heller's myotomy is the ability to perform long myotomies in cases with type III achalasia and other spastic esophageal motility disorders like hypercontractile esophagus and distal esophageal spasm.

Key words: esophagus; achalasia; endoscopy; treatment

Introduction: Achalasia Cardia is a rare neurodegenerative disorder of esophagus resulting in defective peristalsis and impaired relaxation of lower esophageal sphincter (1). Achalasia is rare and the reported incidence and prevalence of achalasia range between 0.03-1.63/100,000 and 1.8-12.6/100,000 persons per year, respectively (2). The incidence of achalasia is rising partly due to increased awareness and utilization of high-resolution manometry (HRM) which is more sensitive in detecting esophageal motility disorders (2, 3).

The pathophysiology of esophageal achalasia is not completely understood, but may involve complex interactions among viruses, immunity and inheritance which ultimately help to progressively destroy myenteric plexus neurons (4). The available modalities for the management of esophageal achalasia do not address the underlying pathophysiologic mechanisms. The available treatment options aim at palliating the symptoms by reducing the lower esophageal sphincter (LES) pressures,

which in turn facilitates the passage of food bolus across esophagogastric junction (EGJ). In these sections we discuss the role of different endoscopic modalities for the management of idiopathic achalasia.

Spectrum of Esophageal Motility Disorders: The latest version of the Chicago Classification (CC Version 4) categorizes esophageal motility disorders into disorders of esophagogastric outflow and disorders of esophageal peristalsis based on the findings of HRM (Table 1) (5). EGJ outflow disorders include achalasia cardia and EGJ outflow obstruction (EGJOO). The disorders of peristalsis include absent contractility, ineffective esophageal motility, hypercontractile esophagus and distal esophageal spasm (DES). Failed peristalsis and elevated integrated relaxation pressure (IRP) are features of all sub-types of achalasia. Type II and III achalasia are further characterized by pan-esophageal pressurization and spastic contractions, respectively in $\geq 20\%$ of swallows (Figure 1). In contrast, IRP

is normal in cases with hypercontractile esophagus and DES.

The manometric subdivision of esophageal motility disorders has prognostic and clinical relevance. The response to endoscopic therapy is inferior in spastic or type III achalasia and other non-achalasia spastic esophageal motility disorders (hypercontractile esophagus and DES) as compared to type I or type II achalasia cardia.

Endoscopic Management Options: The modalities for endoscopic management of achalasia include botulinum toxin (BTX) injection, pneumatic dilatation (PD) and peroral endoscopic myotomy (POEM). Besides these, using fully covered self-expandable metal stents has been described in some studies (6). However, the data regarding their safety and efficacy are limited and their use in the setting of achalasia largely remains investigational.

Botulinum Toxin Injection: BTX injection is being utilized for the management of achalasia for several decades now. BTX inhibits the release of excitatory neurotransmitter (acetylcholine) from pre-synaptic neurons reducing the neurogenic excitation of LES.

Technique: 80-100 U of BTX injection diluted in saline is administered in aliquots of 0.5-1 ml into at least four quadrants (20 U in each quadrant) of LES using a standard sclerotherapy needle. The technique of injection is different in spastic non-achalasia motility disorders (DES and hypercontractile esophagus) where spasms in esophageal body generate symptoms. In these disorders, additional injections at lower thirds of esophagus are recommended (7, 8). A higher dose (>100 U) of BTX injection provides no additional benefit. However, a repeat injection after one-month has been shown to improve the outcomes of BTX therapy (9).

Outcomes: The short-term results of BTX are excellent (70-90% at ≤ 3 months) and nearly two-thirds of patients maintain symptomatic relief at 6-months (10). However, only one third of the initial responders maintain sustained symptom relief beyond 6-12 months (10, 11). The shorter lasting effect of BTX is presumably due to the growth of new axons. The negative predictors for success after BTX injection include young age and a higher baseline LES pressure (12). Therefore, BTX is reserved for elderly and frail patients who are unsuitable candidates for other durable endoscopic or surgical modalities. The major

societal guidelines recommend against the routine use of BTX injection for the management of achalasia (13-16).

Adverse Events: The main advantages of BTX therapy is its excellent safety profile and ease of application. Transient chest pain and heartburn are the most common adverse effects reported after BTX injection (17). Mediastinitis is exceedingly rare after BTX injection, but has been reported and therefore, persistent chest pain and fever after BTX injection should be evaluated further (18).

Pneumatic Dilatation: Using dilatation as a treatment modality was first described by Sir Thomas Willis in 1672 where he used a whale bone to dilate LES. Subsequent attempts with bougie dilators and non-pneumatic balloons were not met with good outcomes. With the availability of low-compliance pneumatic balloons, the outcomes of endoscopic management improved substantially in cases with achalasia.

Technique: The technique is not standardized, and the published protocols differ considerably regarding the inflation metrics including pressure and the duration (8). The most commonly available balloon (RIGIFLEX™ II, Boston Scientific, Marlborough, MA) is made of polyethylene and available in various sizes (30, 35 and 40 mm). In the authors' unit the following protocol is utilized. Initially, the esophagogastric contents are cleared with gastroscopy to minimize the risk of aspiration. Then 1-2 ml of contrast is injected just above the squamocolumnar junction and a stiff (0.038") guidewire is placed into the stomach. Pneumatic balloon is then inserted over the guidewire and positioned across the LES under fluoroscopic guidance. Radiopaque markers on the balloon and the contrast injected in the previous step help in accurate positioning of the balloon across LES. After ensuring the correct position, the balloon is inflated until a pressure of 5-8 psi is reached and the disappearance of waist is confirmed on fluoroscopy. The duration of inflation is dictated by the disappearance of waist which usually occurs within 30-60 seconds of inflation. Post dilatation, the patient is observed for 5-6 hours. Oral liquids are allowed on the same day in cases with no signs and symptoms suggestive of perforation.

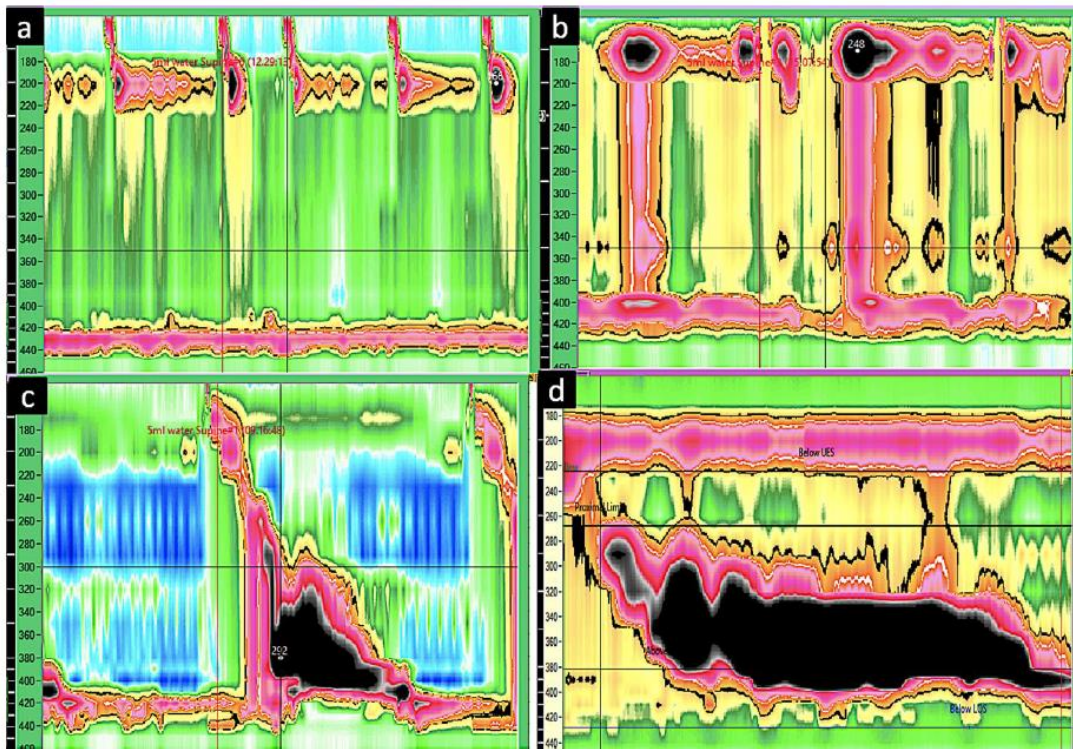
Outcomes: A single dilatation has been shown to provide limited durable response (28% at 6-years) (19).

Table 1: Manometric Classification of Achalasia Cardia and Non-achalasia Spastic Motility Disorders (Chicago Classification V4) (5)

Motility disorder	Defining Criteria
Type I	Elevated IRP (supine and/or upright), 100% failed peristalsis
Type II	Elevated IRP (supine and/or upright), 100% failed peristalsis with PEP in $\geq 20\%$ swallows
Type III	Elevated IRP (supine and/or upright), 100% failed peristalsis and $\geq 20\%$ swallows with spasm
EGJ Outflow Obstruction	Elevated IRP (supine and upright), elevated intrabolus pressure (supine), normal peristalsis, compatible symptoms*, supportive non-HRM test
Distal Esophageal Spasm	Normal IRP, $\geq 20\%$ swallows with spasm, compatible symptoms*
Hypercontractile Esophagus	Normal IRP, $\geq 20\%$ hypercontractile swallows, compatible symptoms*

*Dysphagia and or non-cardiac chest pain; RP, integrated relaxation pressure; EGJ, esophagogastric junction; PEP, panesophageal pressurization; HRM, high-resolution manometry

Figure 1: Manometric Characteristics of Achalasia and Hypercontractile Esophagus



(a) Manometry tracing showing failed peristalsis and elevated integrated relaxation pressures suggestive of type I achalasia; (b) Manometry tracing showing pan-esophageal pressurization in addition to failed peristalsis and elevated integrated relaxation pressures suggestive of type II achalasia; (c) Manometry tracing showing spastic contractions besides failed peristalsis and elevated integrated relaxation pressures suggestive of type III achalasia; (d) Manometry tracing showing high amplitude contractions with normal integrated relaxation pressures suggestive of hypercontractile esophagus.

Therefore, graded dilatation (30 mm followed by 35 and 40 mm balloons) is the standard of care in the current era. After first dilatation, subsequent dilatations with larger balloons are usually performed electively in cases with inadequate relief (20). The European Society of Gastrointestinal Endoscopy (ESGE) recommends dilatation with a 30-mm and followed by a 35-mm balloon after 2–4 weeks. Subsequent dilatation with 40-mm balloon is performed in cases with inadequate relief of symptoms (8). With graded dilatation approach, about 2/3rd patients remain symptom free over 4–6 years. In cases with relapse, “on demand” strategy of dilatation achieves long-term remission in majority (21).

Predictors of Outcomes: The predictors for requirement of repeated treatment include young age (≤ 40 years), male gender, high baseline LES pressure (> 50 mmHg), and incomplete barium emptying ($< 50\%$) after PD (22, 23). Other predictive factors for poor outcomes after PD include wide esophagus (> 3 cm), failed response to initial dilatations, post dilatation LES pressure < 10 mmHg or $< 50\%$ reduction in the LES pressure after PD (23). With the availability of HRM, the manometric sub-type of achalasia has emerged as one of the major prognostic factors for response to PD (24–25). In a study by Pratap and associates, the response rates in type I, II and III achalasia were 90%, 63.3% and 33.3% respectively (24). The results of this study and few other subsequent trials suggest that patients with type II achalasia are best responders, whereas the response is least favorable in type III achalasia. Contrary to the popular belief, inflation time and pressure do not have a significant impact on the efficacy of PD (30).

Adverse Events: The most feared complication after PD is perforation which occurs in 1–3% of cases. A substantial proportion of perforations respond to conservative management (26, 27). Alternatively, closure using endoclips or fully covered metal stents can be performed when recognized early after dilatation. Perforations usually occur during initial dilatations and more frequently while using 35 mm balloon as compared to 30 mm balloon (3.2% vs 1%) (20). In a systematic review including ten studies (643 patients), the rate of perforations was higher when 35 mm balloon was used for initial dilatations (9.3% vs 0.97%, $p = 0.0017$) (20). Using 35 mm balloon for subsequent dilatations instead of initial dilatation is safer with lower rate of perforations. Another risk factor for perforation after PD is age > 65 years (26). Therefore, initial dilatations should be performed using a 30 mm balloon especially in elderly patients.

Per-oral Endoscopic Myotomy: POEM is a relatively new endoscopic modality introduced for esophageal achalasia and other non-achalasia spastic esophageal motility disorders like hypercontractile esophagus and DES. The first series of endoscopic myotomy was reported about four decades ago by Ortega et al in seventeen patients with esophageal achalasia (28). In this study from Venezuela, the authors used a wire type electrosurgical knife to cut the circular muscle fibers at the LES. Although, the results were encouraging this technique was not utilized further presumably due to the risk of perforation and availability of other established modalities i.e., PD and Heller’s myotomy. Nearly three decades later, endoscopic myotomy resurfaced with the introduction of submucosal endoscopy with mucosal flap safety valve technique by Sumiyama and colleagues as a safe way to access peritoneum and mediastinum (29). In the same year (2007), Pasricha and colleagues demonstrated the feasibility of submucosal endoscopy for esophageal myotomy in porcine models (30). The seminal work by Sumiyama and Pasricha paved the way for subsequent trials and Prof. H. Inoue is credited for performing the first POEM in humans (31). Since its introduction about a decade ago, POEM has gradually established its role in the management of achalasia.

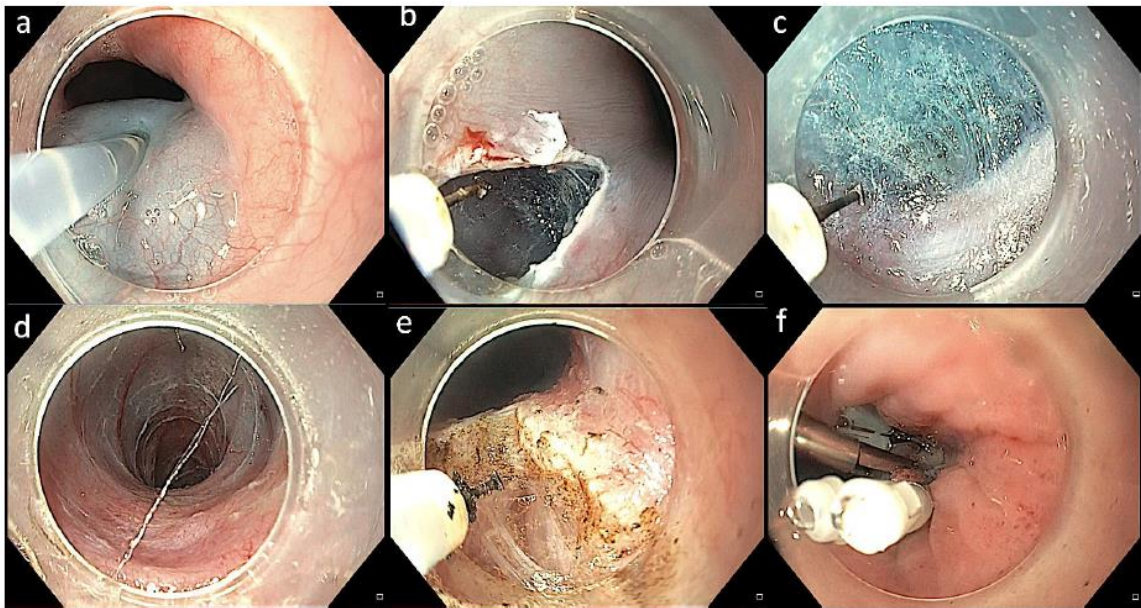
Technique of POEM: POEM is performed under general anesthesia either in an operation room or an endoscopy suite. Initially, the esophagogastric contents are aspirated under light sedation to prevent the risk of aspiration during endotracheal intubation. POEM is usually performed via an anterior (2 O’clock) or posterior (5 O’clock) route. The length of myotomy is decided by the type of achalasia on HRM. A long esophageal myotomy is preferred in spastic esophageal motility disorders including type III achalasia, hypercontractile esophagus and DES (32).

In the author’s unit the following technique is utilized for performing POEM procedure (33). A mucosal lifting injection is given at 6–10 cm above EGJ using a sclerotherapy needle (23 or 25 G) and about 10 cc of diluted indigocarmine. A short (2 cm), longitudinally oriented mucosal incision is made using an electrosurgical knife. Then the submucosal fibers are cleared along the edges of the incision to create space for the entrance of the endoscope in the submucosal space. The submucosal fibers are cleared to create a submucosal tunnel that extends till 2–3 cm across the EGJ. Myotomy is then performed from 2 cm below the lower edge of the mucosal incision till the lower end of submucosal tunnel i.e., 2–3 cm

into the stomach. By this way, a safety flap of mucosa is preserved with intact muscle fibers beneath it enhancing the safety of POEM and other procedures performed using submucosal endoscopy. Finally, the mucosal incision is closed using several endoscopic clips. (Figure 2). Several important modifications in the technique of POEM include the orientation (anterior or posterior) of myotomy and the

length of myotomy (short versus long). Several randomized studies comparing different techniques suggest there is no significant impact of these technical variations on the outcomes of POEM (34-36). However, a short esophageal myotomy reduces the operating time without compromising the safety and efficacy in type I and II achalasia (35, 36).

Figure 2: Technique of Per-oral Endoscopic Myotomy for Achalasia



(a) Mucosal lifting injection using saline mixed with indigocarmine dye; (b) Mucosal incision using triangular knife; (c) Submucosal tunneling; (d) Completion of submucosal tunneling; (e) Myotomy; (f) Closure of incision with endoclips

Outcomes: The efficacy of POEM has been established in multiple studies with short-term follow up (33, 37-39). The short-term clinical success of POEM exceeds 90% in majority of the published literature. Since, POEM is a new modality the data on long-term outcomes are relatively limited. Emerging data suggests the durability of response after POEM and 80-95% maintain remission beyond 4-5 years (40-45). The main advantage of POEM over Heller myotomy is the superior outcomes in type III achalasia and other spastic disorders where a longer esophageal myotomy is required for optimal outcomes (32, 46, 47). Since, the entire esophagus is exposed to the endoscopist, the length of myotomy can be adjusted depending on the esophageal motility disorder.

Adverse Events: Major adverse events are rare after POEM and reported in 1-3% of patients (48). Insufflation related events are common and include pneumothorax (1.2%), pneumomediastinum (1.1%) and

pneumoperitoneum (6.8%). Majority of these are inconsequential and can be easily managed intra-operatively. Other adverse events associated with POEM include mucosal injuries (4.8%), intraprocedural or delayed bleeding, delayed mucosal barrier failure (0.8%) and mediastinitis (48).

The most noteworthy long-term adverse event of POEM is gastroesophageal reflux disease (GERD). The reported incidence of GERD using pH studies and endoscopy ranges from 18-65% and 13-58%, respectively (49). Overall, increased esophageal acid exposure is detected in about half of the patients and reflux esophagitis in about 30-40% of the patients after POEM. The incidence of GERD is higher after POEM as compared to PD and Heller's myotomy plus fundoplication (50, 51). Although, the incidence of GERD is high majority are asymptomatic, develop mild esophagitis (LA grade A or B) and respond well to proton pump inhibitor therapy (52).

Table 2: Pros and Cons of Available Endoscopic Modalities for Achalasia Cardia

	Botulinum toxin Injection	Pneumatic Dilatation	Peroral Endoscopic Myotomy
Efficacy: Short term	30-70% (1-6 months)	90% (3-6 months)	>90% (1-3 years)
Efficacy: Long-term	15-50% (12-24 months)	65% (4 years)* 86% (2 years)** 82-93% (5-10 years)**	80-95% (≥4 years)
Predictors of poor outcomes	Young age, high baseline LES pressure	Young age (≤40 years), type III achalasia, others (see text)	Prior treatment, mucosal injury, reflux, sigmoid esophagus, dilated esophagus (≥3.5 cm), Eckardt score
Complications	Chest pain (16-25%) Mediastinitis (very rare)	Perforation (1-3%), bleeding (2%), GERD (9%)	Mucosal injuries (2-4%), delayed bleeding (<1%)
Indications	Elderly and frail patients unfit for other treatments	Type I and II achalasia preferably >40 years	All sub-types of achalasia especially type III achalasia, hypercontractile esophagus, DES
Advantages	Excellent safety profile, ease of use	Safe and effective Widely available	Durable response, effective in all sub-types of achalasia, more effective PD and HM in type III achalasia
Disadvantages	Limited durability, induces submucosal fibrosis	Multiple interventions required, relatively ineffective in young (≤40 years) and those with type III achalasia	High incidence of GERD, need of expertise

*graded dilatation; **graded and on-demand dilatation

PD, pneumatic dilatation; HM, Heller’s myotomy; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter

Table 3: Selected Randomized Trials Comparing Different Modalities for Achalasia

Study	N	Clinical Success	Adverse Events	Follow-up (Years)	Reflux Esophagitis
Vaezi et al, 1999 (53)	BTX 22 PD 20	32% 70%	NR 5%	1	NR
Zaninotto et al, 2004 (54)	BTX 40 LHM 40	34% 87.5%	10% (mild) 2.5%	2	NR
Boeckstaens et al, 2011 (56)	PD 95 LHM 106	86% 90%	4% 12%	2	19% 21%
Moonen et al, 2016 (57)	PD 96 LHM 105	82% 84%	5% 11%	≥5	14% 18%
Ponds et al, 2019 (50)	PD 66 POEM 64	54% 92%	3% 0%	2	7% 41%
Werner et al, 2019 (51)	LHM 109 POEM 112	81.7% 83%	7.3% 2.7%	2	29% 44%

BTX, botulinum toxin; PD, pneumatic dilatation; LHM, laparoscopic Heller’s myotomy; NR, not reported

Comparison of Available Modalities: The endoscopic modalities available for the management of achalasia include PD, BTX injection and POEM. The outcomes and the pros and cons of each modality have been outlined in Table 2 & 3. BTX injection provides less durable response when compared to PD and Heller’s myotomy (53, 54). The updated Cochrane review including seven studies (178 patients) compared PD to BTX injection and concluded that PD is more effective and durable endoscopic treatment in long-term (>6 months) for patients with achalasia (55). The clinical success was superior in PD group at both 6 (81% vs 52%) and 12 months follow-up (73% vs 37%) (55). Similarly, Heller’s myotomy is a more durable treatment modality as compared to BTX injection (54). Therefore, using BTX injection in the current era is largely reserved for cases which are not suitable for other endoscopic modalities.

PD and Heller’s myotomy have been the mainstay of achalasia management for several decades. The comparison studies between these two modalities suggest that graded PD provides comparable outcomes (56, 57). However, the results of PD depend largely on the protocol of dilatation used i.e., single versus graded and on-demand. In the landmark European Achalasia Trial, clinical success at 2-years was recorded in 86 and 90% of patients in PD and Heller’s myotomy groups, respectively (56). Of note, the dilatation protocol in this study included graded dilatation. In addition, two additional on demand dilatations were permitted after initial series of dilatations in the PD group. But a single dilatation is less durable and inferior to Heller’s myotomy. Graded and on demand dilatation is the accepted strategy in patients where PD is chosen as the treatment modality.

Table 4: Major Societal Recommendations for Endoscopic Management of Achalasia Cardia

	ESGE (13)	ASGE (14)	Seoul Consensus (15)
Botulinum Toxin Injection	<ul style="list-style-type: none"> • BTX can be considered an effective and safe therapy for short-term symptom relief*** • BTX should be reserved for patients unfit for more invasive treatments, or in whom a more definite treatment needs to be deferred.*** 	<ul style="list-style-type: none"> • BTX injection should be avoided as definitive therapy for achalasia patients.*** • BTX injection may be reserved for patients who are not candidates for other definitive therapies.*** 	BTX injection is recommended for achalasia patients whose general condition renders them unsuitable for endoscopic treatment or surgery.***
Pneumatic Dilatation	Graded PD is safe and efficacious treatment for achalasia****	<ul style="list-style-type: none"> • PD is an effective modality for achalasia.**** • PD is preferred over BTX injection for patients with achalasia. **** • PD and LHM are comparable for type I and II achalasia*** 	PD is recommended as an initial treatment for patients with achalasia.***
Peroral Endoscopic Myotomy	POEM is a safe and efficacious treatment for achalasia.****	<ul style="list-style-type: none"> • POEM is an effective modality for achalasia.**** • POEM should be preferred in type III achalasia.* • POEM and LHM are comparable for type I and II achalasia.** 	<ul style="list-style-type: none"> • Outcomes of POEM are comparable to those of LHM for treatment of naïve patients with achalasia.*** • POEM, rather than HM, should be considered for treatment of type III achalasia. ** • POEM is recommended for patients who failed initial endoscopic treatment.*** • POEM can be a rescue treatment for achalasia patients who were not treated successfully by LHM.**

*very low evidence; ** low evidence; *** moderate evidence; **** high evidence

BTX, Botulinum toxin; PD, Pneumatic Dilatation; LHM, Laparoscopic Heller’s Myotomy; POEM, Per-oral Endoscopic Myotomy

POEM has been compared to PD and Heller’s myotomy in several cohort studies and two well-conducted randomized trials. In the randomized trial comparing POEM with PD, POEM outperformed PD with significantly higher clinical success at 2-years follow-up (92% vs 54%, $p < 0.001$) (50). However, reflux esophagitis was more in the POEM group (41% vs 7%; $p = 0.002$).

In another randomized study, Werner and colleagues compared POEM to Heller’s myotomy with Dor’s fundoplication. POEM was non-inferior to Heller’s myotomy at 2-years (83% vs 81.7%). The outcomes of

these trials suggest that POEM may be superior to PD and at least equivalent to Heller’s myotomy.

Societal Guidelines and Recommendations: Several GI societies have published recommendations regarding the management of esophageal achalasia (13-16). The updated version of these guidelines has included recommendations on POEM as well which were missing from the previous iterations. The salient features of the major guidelines for diagnosis and management of achalasia have been outlined in Table 4.

Table 5: Optional Management of Achalasia and Other Motility Disorders

Disorder	Options	Comments
Type I Achalasia	Pneumatic dilatation, Heller myotomy, POEM	Graded dilatation and Heller myotomy are equivalent, POEM found superior to dilatation in one RCT, myotomy preferred in young patients (<40-years), GERD higher after POEM
Type II Achalasia	Pneumatic dilatation, Heller myotomy, POEM	
Type III Achalasia	POEM, Heller myotomy	POEM preferred over Heller in spastic motility disorders
Distal Esophageal Spasm, Hypercontractile Esophagus	POEM	

POEM, Per-oral Endoscopic Myotomy; GERD, Gastroesophageal Reflux Disease; RCT, Randomized Control Trial

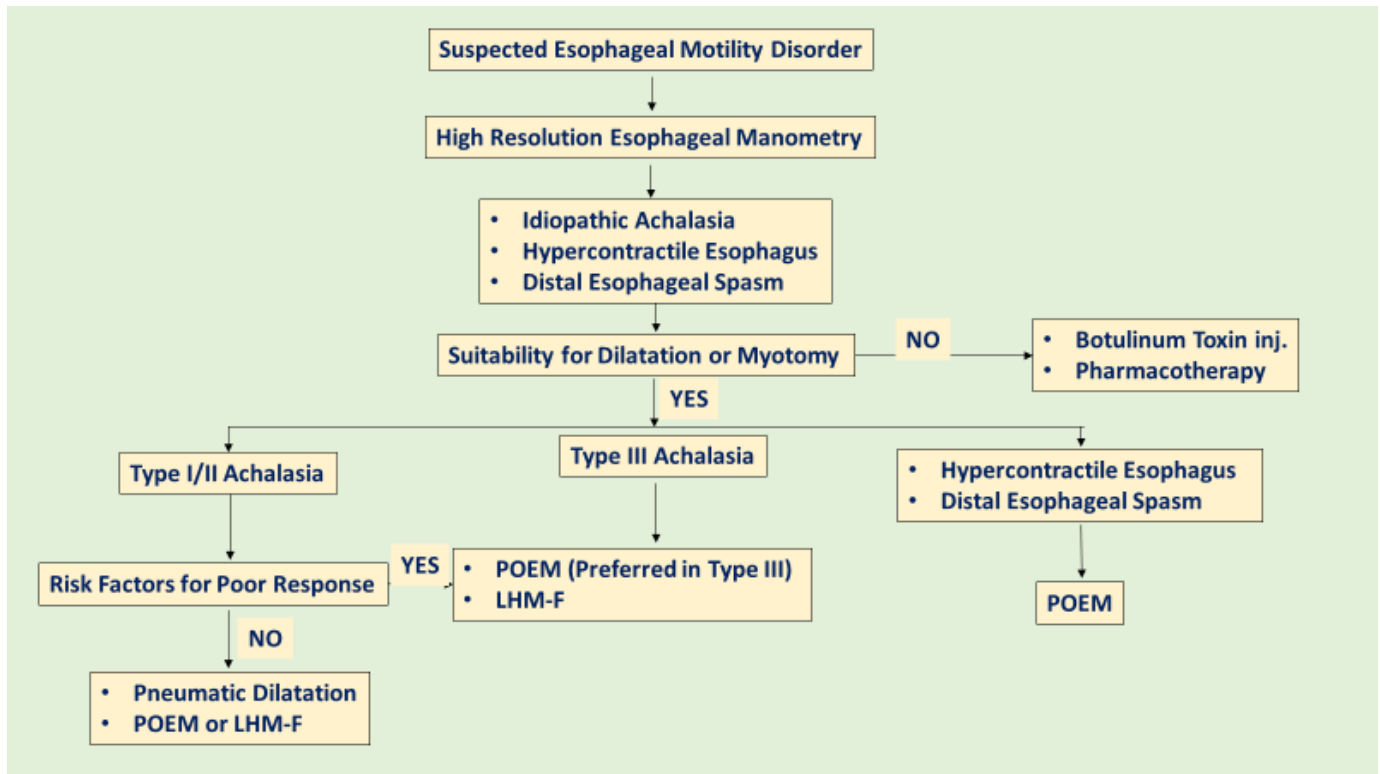
Future Perspectives: The measurement of EGJ distensibility is emerging as a new objective parameter for predicting immediate response after endoscopic treatment for achalasia. EGJ distensibility is measured endoscopically using functional lumen imaging probe (FLIP) which quantifies the luminal dimensions using impedance planimetry (58). EGJ distensibility is reduced in patients with achalasia as compared to healthy controls (59). The distensibility improves significantly in those who respond favorably to endoscopic treatment when compared to non-responders (59, 60). Preliminary data suggests that EGJ distensibility as evaluated using EndoFLIP may be a better parameter than LES pressure for evaluating the clinical efficacy after treatment for achalasia (59).

Although, POEM has emerged as an excellent treatment option for achalasia the issue of GERD remains to be addressed. Novel techniques need to be devised and evaluated to prevent GERD after POEM. The notable contenders include preservation of sling fibers during posterior POEM, endoscopic fundoplication (NOTES-F) and avoiding excess myotomy on gastric side (<4 cm) (61-63).

Summary: Endoscopic management of achalasia has improved substantially over last few decades. PD has been the primary endoscopic modality for over two decades now. Graded PD is an acceptable treatment with satisfactory short and long-term results. With introducing POEM, the armamentarium of endoscopic treatment has augmented further. The safety and efficacy of POEM has been established in multiple studies. With the availability of two effective endoscopic modalities, the treatment of achalasia should be individualized based on patient preferences, availability, and expertise of the operator. In addition, the predictors of response should be considered while selecting a particular endoscopic modality. The manometric type of achalasia and age have emerged as important prognostic factors affecting response to PD. The pros and cons of each of the available treatment options should be detailed to the patients for a shared decision making (Table 5). But BTX injection may be utilized in elderly and frail patients unfit for other definitive therapies (Figure 3).

Disclosure: The authors declare no competing interests.

Figure 3. Algorithmic Approach to the Management of Esophageal Motility Disorders



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Case Report

Adenocarcinoma of Colon in a Six-year-old Child with Birt-Hogg-Dubé Syndrome and Cardiac Rhabdomyoma

Farhana Ali, M.D.¹, Trinh Troung, M.D.¹, Donald Moores, M.D.²,
Kimberly Silva, M.D.¹, and Manoj Shah, M.D.¹

¹Pediatric Gastroenterology, and ²Pediatric Surgery, Loma Linda University School of Medicine,
Loma Linda, CA, USA

Edited by:

Suresh Karne, M.D., Ph.D.
Pavan Kumar Panchavati, M.D., MPH

Reviewed by:

Jennifer Cox, M.D.
Univ. of Mississippi Medical Center
Jackson, MS

Lakshmikanth Katragadda, M.D.
Clearview Cancer Institute
Huntsville, AL

Correspondence:
mshah@llu.edu

Received: February 3, 2021

Accepted: March 25, 2021

Citation:

Ali et al, JAAPI 1(1):42-43, 2021

Introduction: Birt-Hogg-Dubé Syndrome (BHDS) is an autosomal dominant disease characterized by benign skin tumors, renal cell carcinoma, and pulmonary cysts, usually detected in middle-aged persons (1). There are conflicting reports about developing other visceral malignancies, particularly colon cancer, in these patients (2). We report a child with BHDS and heart transplantation for cardiac rhabdomyoma who developed invasive adenocarcinoma of the colon at a very young age.

Case Presentation: A 6-year-old boy who underwent heart transplant at 2 months of age for cardiac rhabdomyoma presented with a 2-month history of worsening profuse watery diarrhea, weight loss, and anemia without associated fever, vomiting, or abdominal pain. Symptoms were unresponsive to changes in diet or immunosuppressive therapy. Extensive initial screening tests for lymphoproliferative, infectious, and malabsorptive causes were negative, except for a mild decrease in fecal elastase. Esophagogastroduodenoscopy and small bowel biopsies were normal. Pancreatic function testing revealed borderline low lipase. Diarrhea did not improve with pancreatic enzyme supplement. Colonoscopy showed rectosigmoid masses (Fig 1), and biopsies had histology consistent with high-grade dysplasia, solid areas of intramucosal carcinoma, and foci of poorly differentiated invasive adenocarcinoma (Fig 2).

Subsequent push-enteroscopy grossly identified multiple nodules and small polypoid lesions in the jejunum with histologic evidence of low-grade and high-grade dysplasia (Fig 3). Gene testing was negative for the *APC* gene (for familial adenomatous polyposis), but whole exome sequencing detected a heterozygous pathogenic variant in the *FLCN* gene consistent with BHDS. The child initially underwent a partial colectomy followed by total proctocolectomy and end ileostomy. He received

chemotherapy postoperatively for colon cancer stage III (1 out of 12 pelvic lymph nodes positive). Two months after completion of chemotherapy, he started losing weight and had fatigue; investigations revealed multiple metastases in the lungs, pancreas, liver, and bones. He did not respond to a second round of chemotherapy and passed away 10 months later (2 years after initial diagnosis).

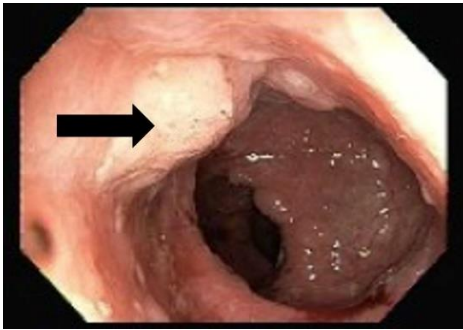


Fig 1: Polypoid lesion with nodularity and ulcer -colonoscopy. Arrow corresponds to findings described in the text.

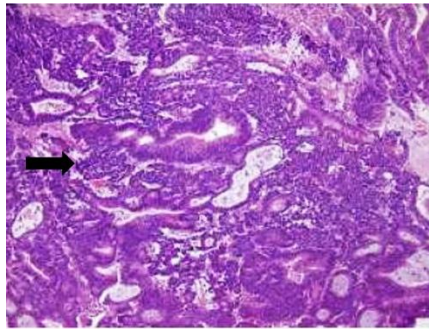


Fig 2: High grade dysplasia and intramucosal adenocarcinoma in rectum. Arrow depicts the findings described in the text.

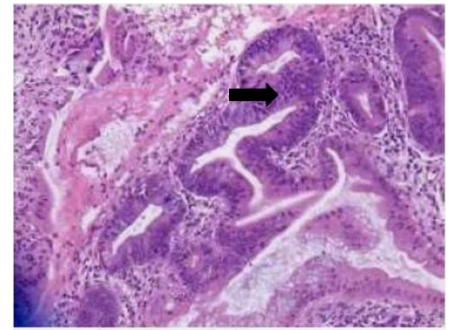


Fig 3: Focal high grade dysplasia in small bowel. Arrow depicts the findings described in the text.

Discussion: BHDS is a rare autosomal dominant condition clinically characterized by skin, pulmonary, and renal findings. Cutaneous manifestations include fibrofolliculomas, angiofibromas, and acrochordons. There may be lung cysts with high risk of spontaneous pneumothorax, as well as various types of renal tumors that are typically bilateral and slow growing (3). The condition is caused by a germline mutation in the *FLCN* (also known as *BHD*, encodes folliculin) gene at 17p.11.2 (4), which has been linked to the mTOR pathway in tumor suppression. There is great variation in *FLCN* expression, and the severity of disease can vary significantly even within the same family. There have been rare reports of other tumor types affecting individuals with BHDS in adulthood, including thyroid cancer, squamous cell carcinoma, Hodgkin lymphoma, rhabdomyoma, and neuroendocrine carcinoma (5). Furthermore, while recent reports suggest BHDS is not associated with colon cancer (6), there have been multiple reports of individuals affected with it (5), such as our patient. These reports may well explain both the cardiac rhabdomyoma and colonic adenocarcinoma in our patient. Our patient is the youngest patient reported with colon cancer in BHDS. It is difficult to comment on the role of immunosuppressive therapy facilitating the early development of colon cancer in our patient.

Conclusion: Birt-Hogg-Dubé Syndrome is an autosomal dominant disorder caused by a germline mutation involved in tumor suppression and is diagnosed by molecular genetic testing for a mutation in the *FLCN* gene. It should be suspected in patients with more than one cancerous or pre-cancerous nidus, even in young children. Colon cancer may develop in these patients even at a young age. The role of immunosuppressive therapy in developing such tumors in these patients is unknown.

Disclosure: The authors declare no competing interests. The patient described here passed away. Parent/legal guardian could not be contacted (? moved). There are no personally identifiable information or images about the patient in this case report.

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Review Article

Breastfeeding Infants and Young Children: Building a Better World

Sandeep K. Chilakala, M.D., and Ramasubbareddy Dhanireddy, M.D.

Division of Neonatology, Department of Pediatrics,
The University of Tennessee Health Science Center, Memphis, TN, USA

Edited by:
Manoj Shah, M.D.

Reviewed by:
Rohit Kohli, MBBS, M.S.
Keck School of Medicine
Univ. of Southern Calif., Los Angeles, CA

Khiet Ngo, D.O.
Loma Linda Univ. Health, Loma Linda, CA

Correspondence:
schilak1@uthsc.edu
rdhanire@uthsc.edu

Received: February 21, 2021

Accepted: April 11, 2021

Citation:
Chilakala and Dhanireddy
JAAPI 1(1):44-50, 2021

Objective: This review summarizes how breastfeeding can positively impact both maternal and child health and lead to several economic and public health benefits. Breastfeeding rates, barriers, controversies, and contraindications in high income countries are compared to low- and middle-income countries (LMIC). Several resources for clinicians, global and national initiatives, and policies are highlighted to overcome challenges of increasing breastfeeding rates.

Introduction: Breastfeeding is the physiologic and biologic norm, benefits maternal and child health, and positively affects national productivity and environmental sustainability (1). "The World Health Organization Innocenti Declaration" in 1998 affirms that all infants should be exclusively breastfed from birth to 4-6 months of age (2). World Health Organization (WHO) recommends initiating breastfeeding in the first hours after birth and infant be exclusively breastfed for the first 6 months. Thereafter it can be continued until two years of age in young children along with safe and adequate complementary foods.

Key Words: Breastfeeding; Benefits of breastfeeding.

The American Academy of Pediatrics (AAP) recommends that infants should be exclusively breastfed for the first 6 months after birth. Solid foods should be supplemented from 6 months to 1 year of age while continuing to breastfeed and it can be continued if mutually desired beyond the first year of age (3). Despite the evidence that feeding breastmilk is associated with a multitude of health and economic benefits, disparities exist in the success of initiation and prevalence amongst various countries (4).

Epidemiology: Globally only 44% of newborns are put to breast within the first hour after birth and 41% are breastfed exclusively for the first 6 months, well below the 90% WHO benchmark (5). In high-income countries, 79% of infants ever receive breastmilk during infancy while this number approaches 96% in LMIC. The prevalence of breastfeeding at 12 months is highest in sub-Saharan Africa, South Asia, and parts of Latin America, while in most

high-income countries, the prevalence is lower than 20% (6).

The U.S. Department of Health and Human Services sets forth national breastfeeding objectives for women every decade. In the United States, breastfeeding initiation rates are about 80% but only 25% of infants are breastfed exclusively for six months; at 1-year only 35.9% infants received any breastfeeding in 2015. *The Healthy People 2030* initiative launched by the U.S. Department of Health and Human Services aims to increase these rates to 42.4% at six months and 54% at one year (7). African American women have the lowest rates of breastfeeding initiation and continuation at 6 months and 12 months, compared to all other racial/ethnic groups in the USA (8). Though breastfeeding initiation rate is increasing globally, it is not being sustained through infancy.

Mortality, Morbidity and Socio-Economic Impacts:

Breastfeeding reduces maternal and child mortality. Scaling up the rate of breastfeeding to a near universal level can prevent about 823,000 child deaths and 20,000 breast cancer deaths every year (9). In LMIC, the mortality risk in infants < 6 months of age who are not breastfed is 3.5 times higher for boys and 4.1 times higher for girls compared to those who received any breast milk (10). In high-income countries, breastfeeding is associated with a 36% decrease in the risk of sudden infant death (11).

Health benefits of breastfeeding for mother and child are summarized in Table 1. Breastfeeding has a substantial

protective effect against childhood conditions such as otitis media, diarrhea, pneumonia and bronchiolitis. Long term, breastfeeding is associated with a 35% reduction in the incidence of Type 2 diabetes mellitus, and a 26% reduction in the odds of developing obesity after correcting for potential confounders. Initial feeding with breastmilk is associated with an increase in intelligence quotient (IQ) by 3 points, improvement in intelligence performance tests 30 years later and increased educational attainment and income in adulthood (12). There is also a 19% reduction in the incidence of childhood leukemia (13, 14).

Table 1: Effects of Maternal Breastfeeding on Infants, Young Children, and the Mother

Infants and Young Children	Mothers
<ul style="list-style-type: none"> • Reduced incidence of otitis media, diarrhea, pneumonia, and bronchiolitis • Reduced incidence of Type 2 DM and Obesity • Increased Intelligence Quotient • Increased educational attainment and income in adulthood • Decreased incidence of Leukemia • Decreased incidence of NEC, late-onset sepsis, growth failure, ROP, and respiratory morbidities in preterm infants • Improved neurodevelopmental outcomes in preterm infants • Optimal colonization and maturation of infant gut microbiome 	<ul style="list-style-type: none"> • Decreased postpartum hemorrhage • Prolonged amenorrhea and birth spacing • Lower depression symptoms postnatally • Reduced incidence of metabolic syndrome, Type 2 DM, hypertension • Reduced incidence of invasive breast cancer and ovarian cancer

Economically a 10%-point increase in the rate of exclusive breastfeeding up to 6 months or continued feeding of breastmilk up to one year translate to reduced treatment costs of childhood disorders by at least \$312 million in the United States. If 90% of the infants in the United States were breastfed, the costs of medical complications would decrease by \$17.2 billion annually (15).

Very preterm infants (<32 weeks’ gestation) are at increased risk of necrotizing enterocolitis (NEC), late-onset sepsis (LOS), growth failure, and death. Mother’s milk has a dose-response relationship in reducing the risk of NEC by about 6-10-fold, compared to exclusive formula feeding. There is also decreased risk of retinopathy of prematurity (ROP), and improved neurodevelopmental outcomes in preterm infants fed mom’s milk (16-20).

Longer duration of breastmilk feeding, often dependent on the socioeconomic status of the household, is associated with reduced incidence of respiratory morbidities among preterm infants (21).

The most important factor that influences the infant’s gut microbiome is mother’s milk. This relationship is complex and mother-baby specific. Breastmilk highly concentrates human milk oligosaccharides (HMOs), a prebiotic, and a diverse bacterial community that facilitates colonization and optimal maturation of the microbiota in the infant GI system (22). Microbiota composition during infancy plays an important role in educating the immune system, metabolic programming and nutrient utilization and has a lasting effect on gut health. The short and long-term benefits of breastmilk are in part due to its effects on gut

microbiome (23, 24). Infants feeding at the breast can alter the microbiome of the milk (25). The effect of breastmilk feeding mode (feeding at breast vs pumping and feeding) on the composition of the infant gut microbiome is unclear. The inability to be fed at the breast and several other factors can make preterm infant's gut microbiota less diverse, less stable, and with lower Bifidobacterium and higher concentration of potential pathogens (24).

Breastfeeding exclusively or predominantly for the first six months has beneficial effects for the mother including decreased risk of postpartum hemorrhage, prolonged amenorrhea, and lower depression symptoms in women with a prenatal diagnosis of depression (11, 26). Decreased incidence of metabolic syndrome, type 2 diabetes mellitus, hypertension (15), and invasive breast and ovarian cancers have been reported in breastfeeding mothers (27).

Barriers, Challenges and Controversies: Challenges to increasing the prevalence of breastfeeding are different among nations. Evidence shows that higher income and education are associated with higher rates of breastfeeding in high-income countries but in LMIC it is the opposite (28, 29). Empowering and encouraging every woman in achieving each country's breastfeeding goals should be a public health priority. Understanding of the many factors affecting the choice of feeding modality is critical to develop interventions for breastfeeding improvement. Women face challenges at home, work, and health facilities along with sociodemographic, institutional, cultural, political, and social barriers that influence, interact, and contribute to low breastfeeding rates.

Community level barriers include knowledge gaps at all levels of health care staff, misinformation, and inadequate breastfeeding support groups. Institutional barriers include healthcare facility practices leading to mother-infant dyad separation, mode of delivery, inadequate lactation consultant support, and free availability of breastmilk substitutes. Societal barriers include negative reactions to feeding at the breast in public. Cultural misperceptions of colostrum being considered toxic, and several other unique cultural misbeliefs exist. At a personal level, maternal education, smoking and drug use, obesity, mental health disorders, lack of support from family and spouse/partner, sexual perceptions, pain and discomfort, and policy level barriers such as inadequate maternal and paternal leave contribute to low breastfeeding rates (30). Providing resources to address these challenges and

barriers and having an individualized support system is essential to increase the prevalence of breastmilk feeding.

Alternative methods to feeding at the breast (pumping, donor milk and milk sharing) are becoming more prevalent and need to be promoted. Expressed breastmilk (pumping) is gaining more importance in the LMIC but there is a lack of guidance and infrastructure to help women who prefer pumping over feeding at the breast (31). Donor breast milk (DBM) use and availability is increasing globally. It is used in preterm infants when the mother is unable to provide her own milk. There is an urgent need to regulate the milk collection process and establish clear guidelines for DBM banking in many countries. Infant formula companies and their aggressive outreach is a major challenge to overcome. Replacement of breastmilk with human milk substitutes has adverse consequences. Keeping this in mind the 4th World Health Assembly in 1981 proposed the International Code of Marketing of Breastmilk Substitutes. Violation of the code is widespread; ineffective legislation and monitoring are major contributors. In the United States, the Special Supplemental Program for Women, Infants, and Children (WIC), despite its positive breastfeeding initiatives, continues to provide free infant formula on a large scale. This is viewed as a conflict of interest. Lack of targeted breastfeeding curriculum in education for physicians and nurses has also been implicated in low initiation rates (32).

Cautions and Contraindications: While breast milk is safe and beneficial for most infants, there are a few cautions and contraindications. Absolute contraindications include mothers infected with human immunodeficiency virus (HIV) living in high-income countries, and infants with classic galactosemia. In LMIC, the benefits of feeding breastmilk may outweigh the risk of acquiring HIV from human milk and exclusive breastfeeding is recommended if replacement feeding is not possible. In infections such as human T-cell lymphotropic virus type I/II and untreated brucellosis, neither feeding at the breast nor expressed breast milk (EBM) is recommended. In untreated tuberculosis, active herpes simplex lesions on the breast, systemic varicella infection, acute H1N1 influenza infection, only EBM is recommended (3). In mothers who are seropositive for Cytomegalovirus (CMV), there is no contraindication to feeding breastmilk to a full-term infant. Although there is a possibility of late-onset sepsis like syndrome in preterm infants (<1500 grams) who are fed with CMV seropositive breastmilk, it is not associated with

abnormal neurodevelopmental outcomes. The benefits of routinely feeding fresh breastmilk from CMV-seropositive mothers to preterm infants are thought to outweigh the risk (33).

Mother to child transmission of Hepatitis B Virus (HBV) via breastmilk is negligible after appropriate immunoprophylaxis. Nursing should be temporarily stopped if nipples are bleeding or cracked in mothers with HBV. Milk should be expressed and discarded until the bleeding has stopped, and the lesions healed (34). There is no evidence that Hepatitis C Virus (HCV) can be transmitted via breast milk. Precautions are similar as for mothers with HBV.

In mothers with opioid use disorder, a comprehensive prenatal and postnatal plan should be in place before encouraging breastfeeding. The mother should be enrolled in a stable methadone or buprenorphine maintenance program prenatally and plan to continue after birth and have a negative screening for HIV and illicit drugs (35). Breastfeeding is contraindicated in mothers who use illicit drugs especially Phencyclidine hydrochloride (PCP) and Cocaine. More information about other drugs including drugs of abuse can be found at LactMed, a database supported by the National Institutes of Health (36).

Smoking is a risk factor and affects the milk supply and health of the infant. Mothers who smoke should be encouraged to reduce smoking and not to smoke around the infant. Cessation modalities like nicotine patch and gum should be discussed with their physician (35). Alcohol will also negatively affect the milk supply and health of the infant. Minimizing alcohol to 0.5 g/kg body weight and waiting at least 90-120 mins after consumption before breastfeeding is recommended (37).

In the United States, breastfeeding a newborn whose mother has COVID-19 depends on the hospital policy of temporarily separating the infant from infected mother vs rooming-in. If temporarily separated, expressed breastmilk should be provided with appropriate respiratory hygiene. WHO recommends skin-to-skin contact, rooming-in and exclusive breastfeeding rather than separating mother and infant (38). Long-term effects of COVID-19 in newborns may not be understood for years. With a lot of uncertainty and everchanging guidelines, clinicians are encouraged to refer to the current guidelines in caring for newborns born to mothers with COVID-19 (39).

Global and National Initiatives to Improve Breastfeeding:

WHO's 65th World Health Assembly (WHA) has set a goal of increasing the rate of exclusive breastfeeding until 6 months postpartum from 38% in 2012 to at least 50% by 2025 (40). The Global Breastfeeding Collective led by UNICEF and WHO in partnership with 20 international agencies was formed to accelerate progress towards this goal. It aims to look beyond the WHA target to 2030, in alignment with the timeline of the United Nation's Sustainable Development Goals (SDGs) (41). Breastfeeding is directly linked to at least four of the SDGs: health, nutrition, poverty reduction and inequity reduction.

WHO and UNICEF launched the "Baby-Friendly Hospital" initiative in 1991 to promote initiation and sustainment of breastfeeding at birthing facilities. The guidelines were revised in 2018. The facility should implement the "Ten Steps to Successful Breastfeeding" (42) and comply with the International Code of Marketing of Breast-milk Substitutes to be designated as a baby-friendly hospital. By 2016, after 25 years of implementation, only 10% of births occur in facilities designated or re-assessed as "Baby-Friendly" (43). In the United States, 18% of birthing hospitals have attained the Baby-Friendly status.

In high-income nations like the United States, racial, socioeconomic, cultural and political differences contribute to the low rates of breastfeeding initiation and sustainment. Overcoming these barriers by providing incentives like paid maternity leave, greater access to breast pumps, social and workplace support, addressing language and cultural barriers, providing education and information will improve breastfeeding rates (44). Following the U.S. Surgeon General's Call to Action to Support Breastfeeding, the Centers for Disease Control and Prevention (CDC) released a summary of successful evidence-based interventions and programs along with action steps to support and improve breastfeeding (45).

A few national campaigns to promote breastfeeding among the women in the USA from racial and ethnic minority groups include, Best Fed Beginnings, Soul Food for Your Baby and The Interconception Care Project for California. Several community coalitions, hospital-based programs, office visits, telephone support, home visits, and community wide interventions are in place to increase the prevalence of breastfeeding. Breastfeeding USA (BfUSA) and La Leche League (LLL) are organizations that provide evidence-based information and support to improve breastfeeding throughout the USA and its territories. They

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use a network of accredited, volunteer breastfeeding counselors and provide a forum to discuss the challenges and ways to promote breastfeeding. Women who want to breastfeed their children can connect with peers via face-to-face meetings, telephone, emails and social media (46, 47).

Support from obstetricians during antenatal clinic visits and before delivery is critical. Guidelines for Perinatal Care by the AAP and The American College of Obstetricians and Gynecologists (ACOG) is an educational resource for clinicians involved in the care of pregnant women, their fetuses and newborn infants (48). The US Preventive Services Task Force also recommends interventions during and after pregnancy to support breastfeeding (49). Initiation of lactation is crucial, and community-based peer counseling by lactation specialists is proven to help women successfully breastfeed. Globally there is a shortage of well-trained lactation consultants. Countries should implement or expand comprehensive training programs

and provide incentives to promote lactation consultant as a career (50).

Conclusions: Breastfeeding is the most cost-effective public health intervention where the mother and the child accrue significant short and long-term physiologic and social health benefits. Countries should continue to assess the progress in their policies and programs to promote breastfeeding and implement actions to bridge the gaps that exist. Promoting breastfeeding is a societal responsibility. Providing accessible, equity-focused, evidence-based breastfeeding support despite race, color, culture, and socioeconomic status is a high-margin investment into the public health system of every country. Policies and interventions at every level should reinforce the message that breastfeeding is natural, optimal, achievable, and results in substantial health and economic benefits to the mother, infant and the society.

Disclosure: The authors declare no competing interests.

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Regulatory Compliance

Basics about HIPAA for Physicians

Ritu Khurana M.D., MLS

Department of Rheumatology
Crozer Prospect Health System
Glen Mills, PA, USA

Edited by:

*Suresh Karne, M.D., Ph.D.
Raj Alappan, M.D., DTCD, DM*

Reviewed by:

*David Klebonis, MSBA
Palm Beach Accountable Care LLC
West Palm Beach, FL*

*Joe W. Campbell, JD
Baker Donelson, Huntsville, AL*

Correspondence:

ritu.khurana@gmail.com

Received: January 24, 2021

Accepted: March 16, 2021

Citation:

Khurana R, JAAPI 1(1):51-55, 2021

What is HIPAA? The Health Insurance Portability and Accountability Act (HIPAA) was a federal law passed in 1996. The HIPAA Security and Privacy Rule establishes national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge. It regulates privacy standards to protect patients' medical records provided to health plans, doctors, hospitals, and other healthcare providers. The Rule states that patient data safety requires healthcare organizations to exercise best practices in administrative security, physical security, and technical security to comply.

Background: The HIPAA Privacy Rule establishes Federal protections for personal health information for all individuals. It establishes a national standard to protect the medical records and other personal health information (PHI), and applies to all health plans, health care billing and clearinghouses, and the health care providers that conduct health care operations electronically.

The Privacy Rule prohibits a covered entity from using or disclosing PHI unless authorized by a patient or their legal health power of attorney, unless this prohibition would unnecessarily interfere with access to quality healthcare or with certain important public benefits or national priorities (like mental health data) (1). It acknowledges that it is essential that the use and disclosure of PHI and all other information are required for easy and ready access to treatment and efficient payment for providers, for effectively operating the healthcare system. Certain legal, financial, administrative and quality improvement operations are essential to support patient treatment and payment in the healthcare system and the Privacy Rule does allow these disclosures. By signing a HIPAA disclosure, all individuals are informed that their health information might be used and disclosed as necessary to treat them, billing for the services provided, and, to some extent, for operating the covered entity's healthcare business. The Privacy Rule does permit a covered entity to use and disclose PHI for treatment, payment, and healthcare operations activities, but with certain limits and

protections, to avoid interfering with an individual's access to quality healthcare.

Main Purpose of HIPAA: The HIPAA Privacy and Security Rule requires that all covered entities maintain reasonable and appropriate administrative, technical, and physical safeguards for protecting electronic PHI (ePHI).

The Three Rules of HIPAA:

- Covered Entities must ensure the confidentiality, integrity, and availability of all ePHI they create, receive, maintain or transmit;
- Identify and protect against reasonably anticipated threats to the security or integrity of the information
- Protect against reasonably anticipated, impermissible uses or disclosures

The Four Primary Objectives of HIPAA Legislation (2):

- To assure health insurance portability by eliminating job-lock due to pre-existing medical conditions.
- To reduce healthcare fraud and abuse.
- To enforce standards for health information.

- To guarantee security and privacy of health information.

A **covered entity** is anyone who provides treatment, payment and operations in healthcare. **Covered Entities** include: Doctor's offices, psychologists, nursing homes, pharmacies, hospitals or home healthcare agencies, health plans and insurance companies. Private Citizens and family caregivers are not "covered" by the Privacy Rule. This means covered entities cannot share patient PHIs with friends or family without a legal power of attorney or a written consent from the patient.

HIPAA's Privacy Rule protects all "individually identifiable health information" (3) held or transmitted by a covered entity, no matter what form it is in. So, HIPAA applies whether a person's health information, including is held or disclosed electronically, orally, or in written form. The HIPAA Privacy and Security Rule requires covered entities to perform periodic risk analysis as part of their security management processes and make changes, as necessary.

HIPAA Legislation: HIPAA Legislation is Organized into Separate "Titles" (4)

Title I: HIPAA Health Insurance Reform: Title I of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects health insurance coverage for workers and their families when they change or lose their jobs. Visit the Centers of Medicare and Medicaid Services (CMS) website for Title I information regarding pre-existing conditions and portability of health insurance coverage.

Title II: HIPAA Administrative Simplification: The Administrative Simplification provisions of the HIPAA of 1996 (HIPAA, Title II) require the Department of Health and Human Services (DHHS) to establish national standards for electronic healthcare transactions and national identifiers for providers, health plans, and employers. It also addresses the security and privacy of health data. Adopting these standards will improve the efficiency and effectiveness of the nation's healthcare system by encouraging widespread use of electronic data interchange in healthcare.

The DHHS develops and publishes rules on implementing HIPAA and standards to be used. All healthcare organizations affected by HIPAA must comply with the standards.

Title III: HIPAA Tax-Related Health Provisions: Title III provides for certain deductions for medical insurance and makes other changes to health insurance law.

Title IV: Application and Enforcement of Group Health Plan Requirements: Title IV specifies conditions for group health plans regarding coverage of persons with pre-existing conditions and modifies continuation of coverage requirements.

Title V: Revenue Offsets: Title V includes provisions related to company-owned life insurance, treatment of individuals who lose U.S. Citizenship for income tax purposes and repeal the financial institution rule to interest allocation rules.

The HITECH Act: The HITECH Act (Health Information Technology for Economic and Clinical Health Act) is part of the American Recovery and Reinvestment Act (ARRA) and was initially signed into law on February 17, 2009. It was created to promote the adoption and meaningful use of Health Information Technology (HIT) and to motivate the implementation of electronic health records (EHR) technology in the United States (5). Upon implementation, the Health Care Providers were initially provided financial incentives for adopting the use of EHR systems to promote the transfer of patient health records in electronic form. The HITECH Act also encouraged healthcare providers to adopt improved privacy and security protections for healthcare data. This was achieved through increased penalties for violations of the HIPAA Privacy and Security Rules. The initial thought was to have comprehensive EHR for individual patients across the country but was impossible due to the availability of multiple EHR platforms. But this has overall led to better and more comprehensive health care data for the patients.

The Omnibus Rule: The Omnibus Final Rule is the most recent addition to HIPAA and was passed to strengthen the protection of PHI and ePHI (6). The HIPAA Omnibus Rule was finalized in January 2013 and went into effect on March 26, 2013. The update improved patient privacy protections and gave individuals more rights for protection of their health information. It assisted with reinforcing the government's ability to enforce the law and apply penalties for noncompliance.

The Omnibus Rule enforces business associates (BAs) and their subcontractors, and it applies to any entity that "creates, receives or transmits" PHI on behalf of a covered entity, may now be held directly liable for impermissible uses/disclosures. It also requires these BAs to report to the

covered entity any security incident of which they become aware, including breach of unsecured PHI. Many individuals and organizations such as billing and credentialing companies and warehouses are considered as business associates (BAs).

Penalties for Violation: The penalties for non-compliance with HIPAA Privacy and Security Rule are issued by the Department of Health and Human Services' Office for Civil Rights (OCR). This includes financial penalties and requires the covered entities to also adopt corrective action plans to bring their policies and procedures up to the standards as demanded by HIPAA. Financial penalties for HIPAA violations were updated by the HIPAA Omnibus Rule, which introduced charges with the HITECH Act. Financial penalties are intended to act as a deterrent to prevent the violation of HIPAA laws, while also ensuring covered entities are held accountable for their actions.

Violation Penalties are based on the Tiers (1-4) of negligence (7) and can range from \$100 to \$50,000 per violation (or per record), with a maximum penalty of \$1.5 million per year for violations of an identical provision (8). Violations can also carry criminal charges that can cause prison time.

The largest HIPAA breach in history was a fine of \$16 million, settled by America's second-largest health insurer Anthem Blue Cross and Blue Shield Association in 2018 (9). This HIPAA breach settlement was to resolve the potential violations discovered during the investigation of the data breach (that saw the records of 78.8 million of its members stolen by cybercriminals) and deter future violations.

The Year that was: "2020": Despite the pandemic, larger healthcare data breaches were reported in 2020 than in previous years since the HITECH Act called for the DHHS' Office for Civil Rights to publish healthcare data breach figures on its website (10).

The year 2020 was a bad one as the Ransomware attacks increased and had a massive impact on all businesses and organizations and not just healthcare in the United States. The year 2020 was a busy year for the Office for Civil Rights (OCR), from Premera Blue Cross's \$6.85 million settlement, the second-largest in OCR history, to various other physicians and health systems and health plans agreed to pay fines towards HIPAA settlements (11).

In March 2020, Steven Porter, M.D., a gastroenterologist in Ogden, Utah, agreed to pay the OCR \$100,000 for a settlement in a potential HIPAA violation related to a data

breach stemming from a dispute with a business associate. OCR determined that Dr. Porter failed to conduct a risk analysis when the breach was reported (12).

In July 2020, Rhode Island based Lifespan agreed to settle a potential HIPAA violation related to a stolen laptop for just over \$1 million, affecting PHI of 20,431 individuals. OCR found that the health system had systemic noncompliance with HIPAA rules, including failure to encrypt e-PHI and a lack of device and media controls (12).

In September 2020, a Community Hospital Systems entity that provides business associate services to hospitals and clinics agreed to settle violations related to a potential HIPAA breach for \$2.3 million. The company provides IT, health information management, and other services to the hospitals and clinics owned by Franklin, Tenn.-based CHS (12).

In September 2020, Athens Orthopedic Clinic in Georgia agreed to pay \$1.5 million to settle HIPAA non-compliance related to a 2016 EHR hacking incident that exposed information of 208,557 individuals. The patient records were posted online for sale by hackers (12).

Also in September 2020, Beth Israel Lahey Health Behavioral Services agreed to pay \$70,000 to settle potential HIPAA violations related to a complaint that an individual could not access her father's medical records (12).

In October 2020, Aetna insurance agency agreed to pay \$1 million to settle three HIPAA violations that occurred within six months in 2017 and affected nearly 18,500 members (12).

Suggestions for Your Practice: A practice that fails to protect its patients' Personal Health Information could face severe penalties and fines and can have far-reaching consequences for years to come. Having to defend yourself against a regulatory violation is an extremely time-consuming process, embarrassing, and leaves a bad reputation for the practice. The most common HIPAA violations are failure to perform a risk analysis to identify risks about confidentiality and integrity of PHI; failure to enter into a HIPAA-compliant business associate agreement; impermissible disclosures of PHI; delayed breach notifications and failing to safeguard PHI (13).

These can cause financial penalties. It makes much more sense to take a preventive approach and put proper technological and administrative protections in place to keep the practice in compliance.

The Office of the National Coordinator for Health Information Technology (ONC), Office for Civil Rights (OCR), and other DHHS agencies have developed several resources for us. These guidelines and educational materials are intended to help us better integrate HIPAA and other federal health information privacy and security into our practice. We must know these critical aspects of a HIPAA compliance program and ensure each is adequately addressed.

HIPAA Checklist (14)

1. Have we distributed the policies and procedures specified to all staff members?
2. Have all staff members read and attested to the HIPAA policies and procedures we have put in place?
3. Have we documented their attestation, so we can prove that we have distributed the rules?
4. Do we have documentation for annual reviews of our HIPAA policies and procedures?
5. Have all our staff members gone through basic HIPAA compliance training?
6. Have all staff members completed HIPAA training for employees?
7. Do we have documentation of their training?
8. Have we designated a staff member as the HIPAA Compliance, Privacy, or Security Officer as required by law?
9. Have we identified all business associates as defined under HIPAA rules?
10. Have we identified all associates who may receive, transmit, maintain, process, or have access to ePHI?
11. Do we have a Business Associate Agreement (Business Associate Contract) in place with each identity we have identified as a Business Associate?
12. Have we audited our Business Associates to make sure they comply with HIPAA rules?
13. Do we have written reports to prove our due diligence regarding our Business Associates?
14. Do we have a management system in place to handle security incidents or breaches?
15. Do we have systems in place to allow us to track and manage investigations of any incidents that impact the security of PHI?
16. Can we demonstrate that we have investigated each incident?
17. Can we provide reporting of all breaches and incidents, whether they are minor or meaningful?

Please make sure there is a system in place, so staff members may anonymously report an incident if the need arises.

Conclusion: HIPAA, HITECH Act, and the Omnibus Rule are the building blocks of Privacy and Security. Understanding these can be an intimidating responsibility. The Department of Health and Human Services (DHHS) and the Office for Civil Rights (OCR) is the main enforcer of HIPAA compliance. The state Attorneys Generals may also play a role in enforcing compliance with the HIPAA Rules. The details of these laws provide a template that can protect physicians and businesses from fines and violations. In December 2020, the Office for Civil Rights (OCR) at the U.S. Department of Health and Human Services (HHS) announced proposed changes to the HIPAA Privacy Rule to support individuals' engagement in their care, remove barriers to coordinated care, and reduce regulatory burdens on the health care industry. I strongly suggest that all Health Care Providers visit the DHHS website periodically for new updates.

Disclaimer: The information in this paper is only a suggestion for your practice and should not be considered legal advice for any purposes.

Disclosure: The author declares no competing interest.

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Focused Review

Cutibacterium acnes: A Potential Etiology for Sarcoidosis

Mina Haghighiabyaneh, M.D.¹, Heather Rojas, M.D.², Ravi Raghavan, M.D., MRCPATH¹

¹Departments of Pathology & Laboratory Medicine, Loma Linda University School of Medicine;

²Veterans Administration Loma Linda Healthcare System, Loma Linda, CA, USA

Edited by:
Sreenivas Chandana, M.D., Ph.D.

Reviewed by:
Prasad S. Garimella, M.D., FAASM, FCCP
Philadelphia College of Osteopathic
Medicine (Georgia Campus) & Gwinnett
Pulmonary Group, Duluth, GA

Lakshmi Kocharla, M.D., FACR
Rheumatology Centers of Western
Michigan, Grand Rapids, MI

Correspondence:
rraghavan@llu.edu

Received: February 5, 2021

Accepted: April 4, 2021

Citation:
Haghighiabyaneh et al,
JAAPI 1(1):56-61, 2021

Abstract: Sarcoidosis is a systemic inflammatory disease, which causes non-caseating granulomas in organs and lymph nodes. The course of the disease is unpredictable and it is typically treated with steroids to reduce inflammation. Despite great understating of pathology and diagnosis of this condition, the precise cause of sarcoidosis is unknown. Recent studies showed several genetic, and environmental factors could be the etiology. In this focused review, we briefly address advances in the triggering factors in sarcoidosis and to be specific, *Cutibacterium acnes*. We review and summarize studies, linking the association between this bacterium and sarcoidosis. We also review the plausible mechanisms of bacteria-induced pathogenesis of sarcoidosis. It is our contention that, identifying etiology will considerably improve the understanding, outlook, and management of this disease.

Key Words: Sarcoidosis; Granuloma; *Cutibacterium acnes*; Triggering factors

Introduction: Sarcoidosis is an enigmatic inflammatory disease, the precise cause of which is unknown. The signature pathologic findings in this disorder consist of non-caseating granulomas in organs such as lungs and mediastinal lymph nodes. In some cases, the heart, nervous system, skin, and other organs can also be affected (1). The disease usually has a chronic course, with unpredictable remissions and recurrences, and is difficult to treat. An uncommon acute form of the disease is called Lofgren's syndrome, where fever, erythema nodosum and joint involvement may also be present at onset (1, 2). The first report of sarcoidosis was from Britain in 1877, at the King's College Hospital, London (3). The disease has a world-wide distribution, with high incidence in the Caucasian population, and Afro-Americans (4), and a lower propensity to affect Asians (1). The first report from India was in 1956 (5).

Sarcoidosis has a variable incidence with age, gender, ethnicity, and environmental factors being determinants

(1). In this report, we focus on some plausible etiologic factors, as there is increasing evidence that infectious agents have a role in the pathogenesis of sarcoidosis. This idea is not new, and it has been investigated in the past. More than one micro-organism has also been linked to the disease (6). Of late, the possible role of *Cutibacterium acnes* (*C. Acnes* – formerly known as *Propionibacterium acnes*), a previously little known agent, has stirred considerable interest amongst investigators. The tentative association was first noted anecdotally more than a quarter century ago (7), but failed to gain attention, until more cases have been reported (1, 6). This caught the attention of some keen Japanese investigators, including one Tokyo-based group of Dr. Yoshinobu Eishi, who launched a comprehensive survey among their patients, and followed up with elegant experiments to explain the possible link (8). Reports in other Asian and European countries followed (6, 8), attracting more attention to this bacterium. Eventually, a large meta-analysis on the topic was published recently, compiling data from 6,000 patients (6).

However, *C. acne* association with sarcoidosis has not received due recognition in North America (9). We intend to examine the scientific validity of this association - as reported by various laboratories - and also present early findings of our own, in support of these claims. This short and focused review will also briefly address advances in triggering factors in sarcoidosis. We contend that identifying etiology will considerably improve the understanding, outlook and management of this disease.

Etiologic and/or Risk Factors in Sarcoidosis: A Brief

Background: Numerous studies have been conducted to unravel the etio-pathogenesis of sarcoidosis, but whatever the cause, the disease is more likely to affect individuals who are genetically prone. This genetic predisposition, as a risk factor, is self-evident in the tendencies for higher occurrence in twins (80-fold), and two- to four-fold increase with affected first degree relatives (1). HLA class II genes, and non-HLA genes have also been implicated. An exciting recent finding is the possible association with mutations in the *NOD2* gene (*Nucleotide binding Oligomerization Domain 2*) as a genetic susceptibility factor for early onset sarcoidosis, which is a part of *Blau syndrome*, a rare systemic inflammatory granulomatous disorder involving skin, joints, eyes and kidneys (1,9). Additional genes (*FCRL1*, *IL23R*) are also implicated in Lofgren's syndrome, an acute form of sarcoidosis characterized by erythema nodosum, bilateral hilar lymphadenopathy and polyarthritits (1).

Multiple lifestyle and environmental risk factors have been looked to, including exposure to mold, and insecticides in farm communities, and occupational exposure to silica dust in industrial settings (10,11). A "sarcoidosis-like pulmonary disease" has been reported amongst rescue workers following the World Trade Center disaster (12). Direct evidence is lacking, but inhaled microbial bioaerosols and inorganic substances may trigger sarcoidosis in susceptible individuals. In contrast, the possible immunomodulatory effect of nicotine in smokers seems to lessen the risk (1). Obesity is a major risk factor, especially in Afro-American women, an ethnic group in which high incidence of sarcoidosis is well recognized (1, 13).

Given the clinico-pathologic similarities to well-known granulomatous inflammatory diseases such as tuberculosis (TB), many early investigators focused on the mycobacteria species as possible culprits or triggering agents (1, 6), even though caseating granulomas (as in TB), are not a feature of sarcoidosis. An increased association with mycobacteria (*M. tuberculosis*) has been reported in sarcoidosis,

compared to healthy individuals, whereas no convincing connection has been established with *Borrelia*, HHV8, or chlamydia (1, 6). Although a direct causal effect has never been established referring to mycobacteria, it is speculated that bacterial remnants may trigger an allergic/auto-immune response (particularly against antigens like mycobacterial catalase-peroxidase [KatG]) (1). Mycobacteria continue to be potential candidates in countries where the disease is endemic, but may not explain the disease elsewhere where TB is uncommon.

Potential Role of *Cutibacterium acnes* in Sarcoidosis:

The most intensely debated agent is *C. acnes*. As the bacterium or its proteins or nucleic acids have been consistently reported in Japanese, Chinese, and European patients with sarcoidosis (8). However, this association has not been adequately explored in North America, especially amongst Afro-Americans (1), and other minorities. In this review, we examined the evidence for this association between *C. acnes* and sarcoidosis. *C. acnes* is a ubiquitous, aerotolerant anaerobic Gram-positive species of propionibacterium that thrives in an anaerobic environment, and found inhabiting in skin, mouth, bowels, conjunctiva, and ears. It has an association with acnes, and an affinity for the pilo-sebaceous elements of the skin (6, 10, 14). Its role in the pathogenesis of sarcoidosis is evolving, and it started with its detection in sarcoid granulomas (4). A related species, *Propionibacterium granulosum* (*P granulosum*), has also been associated with a few cases of sarcoidosis (6, 8). Findings from select case studies from various geographic backgrounds are outlined below, and support the increasing evidence for *C. acnes* and its possible role in sarcoidosis

Case Studies from Asian and European Countries:

Eishi et al reported a body of meticulous experimental work linking *C. acnes* and sarcoidosis (8). In a comprehensive review, they noted that *C. acnes* is perhaps the only pathogen cultured from sarcoid granulomas, albeit sometimes. Their group pioneered in developing a monoclonal antibody, (PAB) that can now detect the bacterium in even archived formalin-fixed paraffin-embedded tissues (FFPE), but also probed sarcoid tissues using in-situ and genomic (PCR-based) techniques (8). In collaboration with other Japanese and international research groups, their laboratory has demonstrated the high prevalence of *C. acnes* in multiple human organs affected by sarcoidosis, often the only micro-organism identifiable in these patients' granulomas within the lungs, lymph nodes, myocardium, and even ocular tissues (8, 15-

20) They have also proposed a plausible pathogenic mechanism linking *C. acnes* and tissue manifestations of sarcoidosis (4). From Europe, there is at least one well documented study demonstrating *C. acnes* in the lungs of sarcoid patients (21). From China, there are at least two published reports that link *C. acnes* to sarcoid granulomas within lymph node lesions (22, 23). A compilation of all the studies from Asia and Europe is shown in Table 1.

Case Studies from North America: Little work has been done in this area in the North America. A notable study came from Robinson LA and associates, who analyzed bacterial DNA by PCR, using formalin-fixed paraffin-embedded (FFPE) tissue from mediastinal lymph nodes in a case series of sarcoidosis. Of the 11 specimens (out of 30), with bacterial DNA, a majority (7) had *C. acnes* (24). Recently, our own laboratory demonstrated *C. acnes* within the brain and mediastinal lymph node granulomas of a patient with sarcoidosis. This is first reported case of neurosarcoidosis with *C. acnes* from the United States of America (25). Detection was made on FFPE sections using the PAB antibody, in collaboration with Dr. Eishi's group. No evidence of any other organisms, including mycobacteria were noted (Figure 1). We later extended the study to additional sarcoidosis patients, and we demonstrated *C. acnes* in at least 8 of 9 specimens with sarcoid granulomas (mostly cutaneous sarcoid), using the same technique, with none showing evidence of mycobacteria or other organisms (unpublished data). Having established that *C. acnes* can be detected in sarcoidosis cases within the U.S. population, plans are under way to expand our sample size, and investigate this intriguing association further. We intend to explore this phenomenon in a much larger series with sufficient ethnic, age, and gender diversity, so the frequency can be better understood in highly vulnerable groups, including African-Americans, Hispanics, and others. Based on these findings, further experimental and/or human studies must establish (or exclude) an etiological role for *C. acnes* in sarcoidosis

Additional Evidence: There is a body of evidence indicating that antimicrobial drugs could improve the clinical effects and granuloma burden in sarcoidosis. This indirectly suggests that a bacterial agent may be etiologically linked to this disease. Measurable response of cutaneous sarcoidosis to tetracycline has been reported by Bachelez et al in a small case series (10 of 12 patients) (26). Another randomized study of 30 patients with cutaneous sarcoidosis revealed significant clinical improvement and reduction in granuloma burden after being administered a

cocktail of antibiotics vs. a placebo for 8 weeks (27). In these studies, no attempt was made to document the presence or absence of any bacteria. Takemori et al, reported a 78-year old patient with sarcoidosis (with biopsy proven granulomas and *C. acnes*) was successfully treated with Clarithromycin (28). In another recent study, 13 patients with cutaneous sarcoidosis (and confirmed *C. acnes* organisms in their tissues), were treated with minocycline. Six of 13 had a complete response and 7 had a partial response (29).

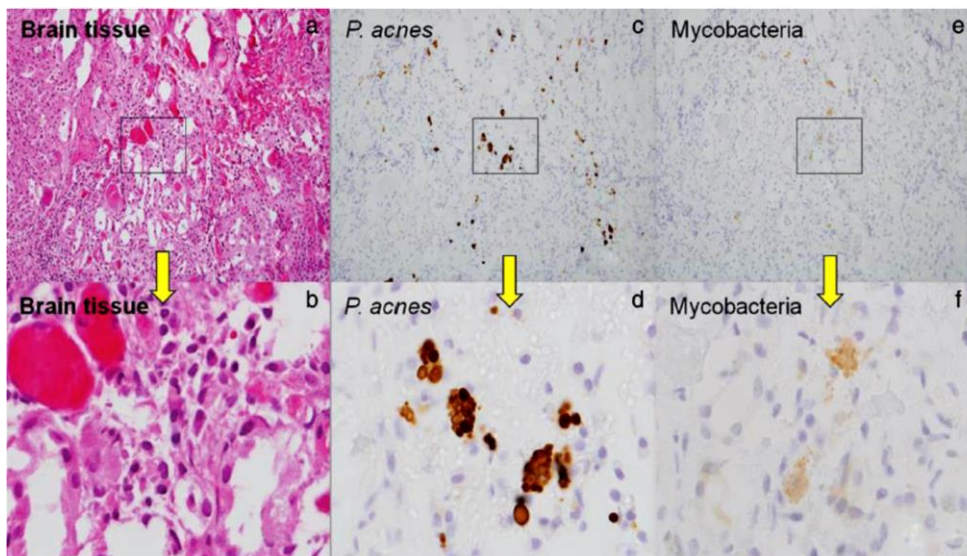
Interesting experimental disease models explore the role of trigger factors (including that of *C. acnes*) in sarcoidosis. Besnard et al., discussed evidence from *in vitro* 3D models, and transgenic mice in their recent review article (30).

From Triggers to Granulomas: It is plausible that more than one agent may have a role in the pathogenesis of sarcoidosis, but accumulating worldwide evidence suggests that *C. acnes* could be associated with sarcoidosis, a potential etiology. Whether *C. acnes* and other bacteria are directly responsible for sarcoidosis is still unanswered. Perhaps one of the best explanations comes from Dr. Eishi's group who believe that the *C. acnes* produces a cellular immune response mainly in individuals, with a hypersensitivity to this bacterial agent (8). They showed that a cell-wall deficient form of *C. acnes* can remain latent in susceptible people, and may get endogenously re-activated under specific conditions, leading to a granulomatous response (4). This idea was tested in mice sensitized with the *C. acnes* protein, which developed pulmonary granulomas only if they had latent/dormant infection; whereas eradication of the infection with antibiotics did not generate granulomas (4). At a cellular level, the sequence of events in the immune response that leads to sarcoid granulomas has been extensively studied, and in a recent review by Grunewald et al., the following hypothesis was put forward (1). It seems a cascade of events is possibly triggered in a step-wise fashion by environmental factors (bacterial infections like *C. acnes*, *Mycobacterium tuberculosis*, or other agents (known and unknown). These interact with genetic/epigenetic factors in vulnerable people, leading to innate immune activation of macrophages and dendritic cells, upregulation of MHC class antigens and cytokines. The next stage seems to be upregulation of *mTORC1* (mechanistic target of rapamycin complex-1) pathway, serum amyloid A (SAA), and heat shock proteins/HSP. Finally, there is SAA aggregation in granulomas, and enhanced T-cell responses, which in the presence of

Table 1: Case studies supporting *C. Acnes* involvement in sarcoidosis from Asia and Europe.

Authors	Country	Organ tissue	Technique/ Test	Result/ Conclusion
Ishikki et al. ⁵ 2019	Japan	Lung tissue	Immunohistochemistry using a <i>C. acne</i> antibody in FFPE tissues	Demonstrated <i>C. acne</i> within pulmonary granulomas of a patient treated sarcoidosis patient treated with the TNF inhibitor, etanercept for rheumatoid arthritis, suggesting that even drug-induced sarcoidosis had an association with the bacterium
Suzuki Y et al. ⁶ 2018	Japan	Lymph node	Immunohistochemistry using a <i>C. acne</i> antibody in FFPE tissues	Identified <i>C. acne</i> associated immune complexes within sinusoidal histiocytes of 89% of lymphadenitis cases, compared to 20% in non-sarcoid lymphadenitis cases, and none in controls
Asakawa N et al. ⁷ 2017	Japan	Cardiac tissue	Immunohistochemistry using a <i>C. acne</i> antibody in FFPE tissues	Cardiac tissue samples from sarcoid patients with severe inflammation had <i>C. acne</i> compared to non-sarcoid myocarditis, and cardiomyopathy controls
Goto H et al. ⁸ 2017	Japan	Ocular tissue	Immunohistochemistry using a <i>C. acne</i> antibody in FFPE tissues	Identified <i>C. acne</i> in 4 of 10 patients with ocular granulomas; the ones without granulomas were negative
Minegishi K et al. ⁹ 2015	Japan	Whole genome sequence from the C1 strain of <i>P. acnes</i>	Core genome analysis and multiple genome alignment	C1 strain of <i>C. acne</i> was the primary bacterial isolate from sarcoid granulomas and ST26 strain was the likely causative agent in sarcoidosis
Negi et al. ¹⁰ 2012	Japan	Lung and lymph node	Immunohistochemistry using a <i>C. acne</i> antibody in FFPE tissues	Recognized <i>C. acne</i> within lung and lymph node granulomas of sarcoid and none in a control group of non-sarcoid tuberculous granulomas
Schupp JC et al. ¹¹ 2015	Germany	BAL fluid	IgG- and IgA-ELISA	BAL cells of sarcoidosis patients expressed high levels of inflammatory cytokines such as TNF, and GM-CSF when stimulated by heat-killed <i>C. acne</i> and BAL fluid of sarcoid patients had higher IgG & IgA levels to <i>C. acne</i> .
Zhao MM et al. ¹² 2017	China	Lymph node	High throughput 16SrRNA sequences	Showed abundance of <i>C. acne</i> within lymph nodes of sarcoidosis patients
Zhou Y et al. ¹³ 2015	China	Lymph node	RT-PCR	Demonstrated high levels of <i>C. acne</i> or <i>P. Granulosum</i> rRNA in 48 of 65 sarcoidosis samples from lymph nodes, as compared to 4 of 45 tuberculosis cases, and 3 of 50 controls

Figure 1: *C. acnes* in Neurosarcoidosis



Figs.1a & 1b show sarcoid granulomas in the brain (a: low-power & b: high power; H&E stain); Figs.1c & 1d show *C. Acnes* within sarcoid granulomas in the brain (c: low-power & d: high power; PAB immunostain); Figs.1e & 1f show absence of mycobacteria within sarcoid granulomas in the brain (e: low-power & f: high power; M. tuberculosis immunostain). From Yang et al (25) with permission.

interleukins (IL- 6, IL-12 and IL-18) and TGF-β (transforming growth factor-beta), leads to an ineffective or impaired T cell response. The triggering antigens might, however, persist, leading to a chronic inflammatory disorder.

Conclusions: To conclude, this brief and focused review has attempted to summarize how sarcoidosis starts and evolves in humans. Evidently, more than one etiologic agent may trigger the disease. Genetic predisposition and

environmental factors may play a role in modifying the outcome. However, *C. acnes* may be the most prevalent infectious agents associated with this condition, worldwide. The handful of studies indicating at least

limited success with antibiotic therapy also imply a role for infectious agents, and it needs further evaluation.

Disclosure: Authors disclose no competing interests.

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Brief Report & Analysis

PACS: Post-Acute COVID-19 Syndrome

Kavitha Das, B.D.S., M.P.H., M.S.¹, and Seshadri Das, M.D.²

¹Department of Cardiology; ²Endocrinology, Diabetes and Bone Diseases,
Mount Sinai Hospital, New York City, NY, USA

Edited by:
Niharika Khanna, M.D., DGO

Reviewed by:
Pradeep Garg, M.D.
*Univ. of Maryland Baltimore-
Washington Medical Center
Pasadena, MD*

Rakesh Vinayek, M.D.
*Sinai Gastroenterology Associates
Baltimore, MD*

Correspondence:
kavithapdas@caa.columbia.edu

Received: February 21, 2021

Accepted: April 21, 2021

Citation:
*Das K and Das S
JAAPI 1(1):62-66, 2021*

Background: The novel Coronavirus 2019 disease was declared a global pandemic in March 2020 (1) and it resulted in disrupting normal life as we knew it (2). It's been reported that globally there have been over 140 million COVID-19 cases, and 79.5 million have recovered from COVID-19 (3). According to the U.S. Centers for Disease Control and Prevention (CDC), over 566,000 COVID-19 deaths occurred in the United States and 31.6 million people were infected (4). At present, there are limited data available on post-COVID-19 sequelae (5). In patients who recovered from COVID-19, disease diagnoses related to multiple organ systems were reported. These sequelae left unchecked and untreated can lead to a public health crisis. Strategic approaches to assess, prevent and treat Post-Acute COVID-19 Syndrome (PACS) or Long COVID has been recommended by the National Institutes of Health at a high-level national meeting held in December 2020 (5). This article is a brief report on PACS and a summary of the NIH report on a virtual workshop conducted on December 10th, 2020 on Post-Acute COVID-19 Syndrome (5).

Working Definitions: There is no consensus on a clear definition for PACS yet. The definition varies depending on the severity of illness and symptoms.

1. The CDC defined PACS as sequelae that extend beyond 4 weeks after onset of initial infection (6,7). CDC described hyper inflammation that occurs in multiple organ systems due to COVID-19, and called it the multisystem inflammatory syndrome (MIS). This syndrome is called MIS-C in children and MIS-A in adults (6, 8, 9). The hyper inflammation seen in COVID-19 acute infections in adults is harder to differentiate from other symptoms. Thus, there are more data on MIS-C (6).

2. PACS has also been defined as the syndrome that starts after a patient is discharged from inpatient acute care. These patients have been hospitalized for over 3 weeks after the initial onset of symptoms (10).

3. Datta et al broke down the disease into 3 categories at the population level: (a) The acute COVID-19 phase; (b) the post-acute hyperinflammatory phase that includes MIS-A

and MIS-C; (c) a late inflammatory and virological sequelae or PACS (6).

Description: There are limited data on the prevalence, length of disease, underlying causes, and effective management of PACS symptoms (11). PACS categories include asymptomatic, mild, moderate, severe, and critical forms of the disease. It has been recommended that the clinical management of PACS should include an all-inclusive approach that treats the patient as a whole (7). Persistent symptoms of PACS in hospitalized patients are seen in multiple organs and multiple systems. Symptoms include fatigue, difficulty in breathing, chest pain, sleep disorders, anxiety, cough, headaches, sore throat, loss of smell and taste, and insomnia (12, 13).

According to Carfi and colleagues, 87% of the patients who had recovered from COVID-19, reported at least 1 symptom of PACS (12). An article from the Morbidity and Mortality Weekly Report stated that 35% of symptomatic non-hospitalized COVID-19 patients did not return to

baseline health 2 to 3 weeks after testing positive (14). Non-hospitalized COVID-19 disease can cause lengthy illness and enduring symptoms even in young adults. Older adults and patients with comorbidities were associated with lower health status when compared to their pre-COVID-19 health status (5).

In adults between the ages of 18 to 34, and in those with no comorbidities, 19% had not returned to baseline health (14). Statistically significant differences were not seen in health-related quality of life of ICU versus ward patients, but a reduced proportion of patients from the ICU returned to work after an average of 110 days post-hospital admission (13). It has been suggested by Batlle and the NIH, that organ crosstalk between the injured organs like the lung, the heart, and the kidney can explain PACS (5, 15).

There is a paucity of data on the clinical course of PACS for individuals with a milder, outpatient manifestation of the disease when compared to those with acute forms of this illness and more data are needed.

Sequelae of Post-Acute COVID-19 Syndrome in Adults: Based on limited data available, PACS seems to affect patients manifesting different levels of severity of the disease; it affects multiple organ systems, all genders, and affects all ages including unique sequelae seen in children. Some have suggested that psychiatric changes, difficulty in breathing, alopecia, and fatigue are seen more frequently in women but additional data are needed (16-18). The most common lingering symptoms are fatigue, muscle weakness, breathlessness on physical exertion, headaches, sleeplessness, anxiety, depression, loss of taste and smell, anxiety, and chest pain (5, 11-13, 10, 20).

CVD and Diabetes. It was reported that cardiac magnetic resonance imaging revealed cardiac abnormalities in over 60% of study participants (19). This was independent of the duration of initial diagnosis, the severity of COVID-19, and progression of acute illness (5, 19). Biopsies revealed inflammatory infiltrates (19). Autopsies conducted in one study presented the COVID-19 virus in the myocardium in the majority of the cases, and it showed evidence of viral replication (21). Changes in cardiac tissues were not limited to older adults. Fifteen percent of Ohio State University athletes had myocarditis after mild COVID-19 illness, and half had CMR (Cardiovascular Magnetic Resonance) abnormalities (5, 22). Additional research is needed in this area to study the impact of COVID-19 in young athletes and young adults.

In Wuhan, China, in 42% of the fatalities, the patients had diabetes as a comorbidity (23). The reason for higher mortality in diabetic patients is not well-understood (24). It may be related to characteristic immune functions (25). Type 2 diabetes patients are predisposed to cardiovascular diseases and are older which may explain increased fatalities in diabetic patients (24).

Respiratory Related Illness. Fatigue and breathlessness were seen in 60% of the ward patients 4 to 8 weeks after being released from the hospital, according to Halpin and colleagues (26). This was also seen in 72% of the ICU patients for the same duration by the same authors. The authors recommended that post-recovery rehabilitation might be necessary for some of these patients.

Even in patients with non-acute COVID-19, persistent dyspnea was seen in 37% of patients at 30 days and 30% of patients at 60 days (27). Radiological abnormalities were seen in 71% of patients after twelve weeks post-hospital discharge (28). Lung function abnormalities were seen in 25% of the patients 3 months after hospital discharge in non-critical patients (28). A retrospective study from China found that spirometry pulmonary function was impaired one month after hospital discharge in over 50% of the patients (29). The same study reported debilitated diffusing-capacity, lower respiratory muscle strength, and lung imaging abnormalities in over 50% of patients in an early recovery phase. Patients with severe disease had a higher incidence of diffusion lung capacity for carbon monoxide impairment than patients with less severe COVID-19 illness (29). Subjects with a severe form of illness were usually hospitalized and had more severely impaired pulmonary diffusion capacities and abnormal chest imaging (17).

Mental Health. New diagnoses of anxiety, insomnia, dementia and mood disorders, and other cognitive impairments and psychiatric disorders, were increased after COVID-19 illness (11, 17, 30). The NIH also reported rare side effects including symptoms similar to multiple sclerosis, Parkinson's-like symptoms (5), and symptoms similar to Guillain-Barre Syndrome (31, 32). Long term impact of PACS in patients with COVID-19 and CNS involvement have shown symptoms termed as 'brain fog'. Brain fog includes psychological symptoms, behavioral changes, cognitive impairment, confusion, and poor concentration (39). These cognitive changes associated with long COVID-19 will affect the prognosis of disease, and long-term care. Therefore, there will be a higher need

for access to mental healthcare for cognitive issues related to PACS.

Sequelae of Post-Acute COVID-19 Syndrome in Children and Adolescents- Multi-System Inflammatory Syndrome: Children are less affected than adults in the United States (33). However, many children with COVID-19 antibodies have developed severe inflammatory conditions with Kawasaki disease features (34). The majority of these had no underlying conditions and 80% required ICU care (33). MIS-C requires vigorous medical intervention with a multidisciplinary team and closely monitored long-term follow-up. The most commonly seen symptoms in children 2 months after the onset of COVID-19 were fatigue, dyspnea, and heart palpitations or chest pain (38).

Public Health Impact of PACS: It has been reported that higher numbers of patients with pre-existing chronic conditions, may cause longer recuperation time from symptoms of COVID-19 (20). The NIH predicts that several thousand people will probably suffer from PACS and early interventions will aid in reducing the disease burden (5). Testing coverage for COVID-19 has varied globally (20, 35). It has been reported there is a possibility of underreporting of COVID-19 cases (20, 35, 36), and subsequently an increase in PACS cases is likely that might go undiagnosed. Studies on SARS patients showed that many patients exhibited chronic fatigue and psychiatric problems 1 to 3 years post disease diagnosis (34, 37). The involvement of multiple organ systems necessitates the need for in-depth clinical research at local, national, and international levels to mitigate the impact of PACS (5, 24). Having a strategic approach to reduce the burden of disease on the health care system and improve the health-related quality of life is recommended based on evidence-based research.

Conclusion: The emphasis in the past has been on the acute phase of COVID-19 and there are limited data on long-term sequelae of COVID-19. Follow-up studies in recovered COVID-19 patients from all age groups, socio-economic backgrounds, pre-existing health conditions, and different severities of the disease spectrum are needed to study the long-term impact of the disease. Evidence is needed to establish standards of care for PACS to help treat the disease. Integrated rehabilitation is recommended for COVID-19 patients. Rehabilitation should be customized based on the needs of the patient. Education on the potential long-term consequences of the disease is needed to enroll patients based on disease severity. ICU

COVID-19 patients will need a more comprehensive approach to rehabilitation when compared to patients with milder forms of the disease. Care for long-term sequelae of COVID-19 will require a multi-disciplinary, multi-tiered, and long-term approach to minimize disease burden on individuals and healthcare systems. Long-term care can include clinicians, mental health providers, occupational therapists, social workers, and virtual and in-person support groups. Dissemination of resources should be made public and widely available to providers and patients. A systematic, integrated, long-term approach will aid in reducing the long-term global burden of this disease.

Disclosure: The authors declare no competing interests.

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Review Article

The Aging Kidney: Pathophysiology and Clinical Implications

Bellamkonda K. Kishore, M.D., Ph.D., MBA

Division of Nephrology & Hypertension, Department of Internal Medicine;
Department of Nutrition and Integrative Physiology; Center on Aging
University of Utah Health, Salt Lake City, Utah, USA

Edited by:
Raj Alappan, M.D., DTCD, DM

Reviewed by:
Kasinath Balakunthalam, M.D.
University of Texas Health,
San Antonio, TX

Fernidand Alcaide, M.D.
Renal Associates, LLC,
Columbus, GA

Accepted by:
Vemuri S. Murthy, M.D., M.S.
Editorial Advisor

Correspondence:
BK.Kishore@hsc.utah.edu

Received: February 9, 2021

Accepted: March 18, 2021

Citation:
Kishore BK,
JAAPI 1(1): 67-75, 2021

Abstract: According to the World Health Organization, by 2025 one in 10 adults in the world will be 65 years or older. This emphasizes the importance of gerontological research and geriatric medicine in global healthcare. With increasing life expectancy worldwide, understanding the aging process and caring for the elderly are bound to move to the forefront in all branches of medicine and healthcare in the 21st century. Although all organs age naturally, heart, lung and kidneys stand out, as they show large decline in age-associated function. The presence of comorbid conditions, such as diabetes mellitus and hypertension, accelerates aging of the kidney. Our knowledge of aging process itself and how comorbid conditions influence aging of individual organs is still work in progress. Unlike animal models of aging, where aging process is relatively free from comorbid conditions, human studies on aging are confounded by several variables, which are often intermingled with each other. Longitudinal studies on human aging are not within reach for many investigators. This review, which is tailored for physicians, presents a comprehensive picture of aging process as we understand it, the problem of atypical clinical presentation in elderly subjects, structural and functional changes in the aging kidney and their clinical implications, the role of cellular senescence in promoting age-associated kidney diseases, role of dietary and pharmacological factors in aging kidney, age-associated defects in water and sodium homeostasis and the clinical trials of drugs promoting healthy aging.

Key Words: Chronic Kidney Disease; Acute Kidney Injury; Cellular Senescence; Nephrotoxicity; Water Homeostasis

Prologue: According to the World Health Organization, by the year 2025 there will be 800 million people above 65 years worldwide, when the global population is expected to reach 8.18 billion. That is 1 in 10 persons will be an elderly one. This essentially makes geriatrics to percolate into every branch of medicine. All organs lose their functional capacity due to aging. However, the biggest change in the functional capacity occurs in the heart, lung, and kidneys. While an elderly person can often feel the symptoms of an aging heart or lung, an aging kidney is silent until it fails. Even from the clinical viewpoint, assessing aging kidney function and reserve capacity is not easy. Added to that, comorbid conditions, such as diabetes mellitus or hypertension markedly influence the natural aging process of the kidneys, often in a variable manner among different individuals. Hence, in this review we focus

on the aging kidney and its pathophysiological and clinical implications.

What is Aging? Aging is defined as **CUPID**, which stands for Cumulative (changes that occur throughout life), Universal (nothing is exempt from the aging process), Progressive (changes occur gradually over time), Intrinsic (happens within the body with/without external influence), and Deleterious (leads to a decrease in functional capacity) (1). There is a distinction between aging and age-associated diseases. Unlike aging process, age-associated diseases lack universal quality. Aging is a consequence of two associated, but not identical processes. These are decline in function, and reduction in adaptive capacity. Until recently it was considered that aging is a natural process. However, as we can see later in this article, in recent years this has been increasingly challenged and

evidence is accumulating to show that aging is a sort of disease that can be reversed with interventions.

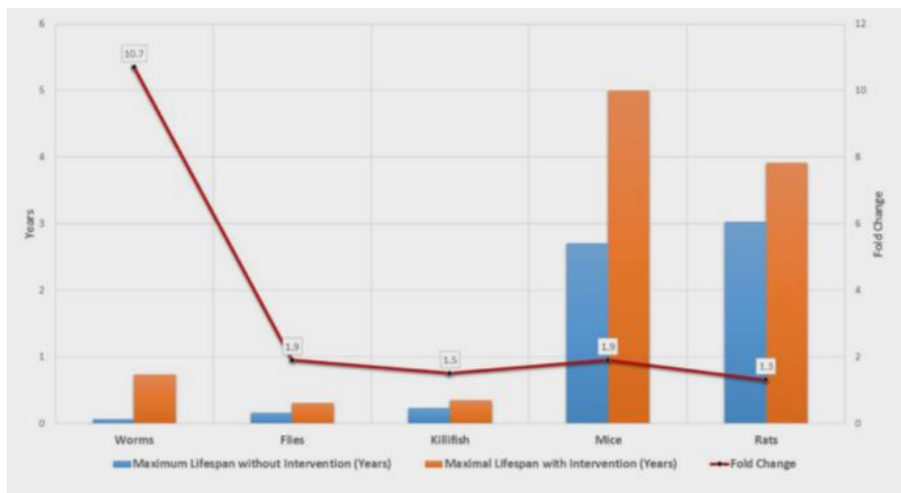
Atypical Clinical Presentation in the Elderly: Atypical presentation in the elderly is defined as presentation with a disease state missing some features considered traditional for that illness in younger patients. This is vague or altered presentation of an illness, or non-presentation of illness. Age affects clinical presentation in the elderly subjects so much, it often calls for special skills to deal with it. This is due to (i) intrinsic factors, such as aging, nutrition, mood, and cognition; (ii) extrinsic factors, such as pharmacological, social, and financial ones; or (iii) geriatric giants, namely incontinence, inability, instability, and intellectual impairment (the four Is). Failure to recognize atypical presentations in elderly patients may have serious consequences, such as missed diagnosis or missed opportunities to treat common conditions (2). Because of these, atypical medical presentations in the older subjects are now an Accreditation for Graduate Medical Education (ACGME) in Geriatrics competency. Geriatric assessment, which calls for a multifunctional, multidisciplinary approach specifically designed to evaluate functional ability, physical and mental health, cognition, and socioenvironmental circumstances of older subjects is becoming a necessity rather than an option (3). For example, atypical presentation of illness in elderly subjects in emergency departments may have worst outcomes (4). A report from Hunan Province in China presented evidence that elderly patients with COVID-19 are likely to have atypical presentation without fever or cough (5). Due to gradual loss of liver and kidney functions, the pharmacodynamics of medications is altered in older subjects, resulting in side effects of drugs mimicking symptoms of many diseases. This can lead to diagnosis of illnesses that may not exist in older subjects. The WHO Global Patient Safety Challenge Medication Without Harm recognizes medication-related harm (MRH), as a geriatric syndrome (6). These and other similar studies emphasize the importance of recognizing atypical presentation of diseases by elderly patients even in disciplines other than geriatrics, especially considering that one in 7 in the United States (or 50 million people) are above 65 years old.

Theories of Aging Process: There are three main theories of aging process. These are: (i) Exogenous or environmental theory, (ii) Genetic theory; and (iii) Mixed theory (1). The exogenous or environmental theory proposes that genetic factors are not involved in the aging process. But, multiple environmental factors, such as diet

or derivatives of metabolism (e.g., advanced glycation end products or the AGEs on nucleotides, lipids, and peptides/proteins) cause insults that result in cellular senescence leading to aging process at the whole organism level (7). The exogenous theory surmises that damage caused by environmental factors is limited to macromolecules in the cell, but it does not affect DNA in the nucleus. But the genetic theory proposes that aging is genetically programmed, and its phenotypic manifestation depends on expression of genes at time. Thus, the genetic theory assumes that aging process is deterministic, and the rate of progression of aging is genetically preprogrammed at birth. However, there is difference of opinion among scientists whether aging process is constitutively coded in the DNA of every cell or it is manifested in the genetic material of functional entities such as nervous or endocrine systems. The mixed theory proposes that repetitive environmental insults can cause alterations in the genetic structure and/or function. Each organism has a genetic propensity for aging, which can be modified by exogenous factors or the own metabolism of organism (8). This is further supported by the population-based Swedish Twin Registry study, which revealed that a maximum of one third of variance in longevity is attributable to genetic factors, and the remaining variance was due to nonshared, individual specific environmental factors (9). Because of these studies, many gerontologists believe that aging is due to an interaction of several factors, such as heredity, environment, culture, diet, exercise, leisure, and illnesses.

Is Aging a Natural Process or Disease? In recent years, experimental data from animal models are raising questions whether aging is a natural process or disease. Biogerontology Research Foundation, a charitable organization based in the United Kingdom, and supports the application of knowledge of mechanism of aging to the relief of disability, suffering and disease in old age, argues that aging is a disease. The foundation also presents intriguing data from animal models supporting its standing on aging (Fig 1). In this respect, animal models offer better perspective than humans, as the former do not have comorbid conditions associated with aging. Biodemographers, a new generation of researchers, are demanding that aging should be officially recognized as a disease and should be given its individual code in the International Statistical Classification of Diseases and Related Health Problems (10, 11)

Fig 1: Animal Models Offer Better Perspectives for Aging Research, as They are Free from Comorbid Conditions that Affect Aging Process as We see in Humans.



As shown in this figure, in five species of animals namely (Lt to Rt), worms, flies, killifish, mice and rats, interventions to slowdown aging process prolonged the lifespan. For each species studied, the blue bar shows lifespan without interventions and red bar gives lifespan with interventions. These data support the argument that aging is a disease. If aging is not a disease, but a natural biological process, the interventions should not prolong lifespan. Reproduced from Bulterijs et al, 2015 (ref # 10; Open Source: Creative Commons Attribution 4.0 International)

The Aging Kidney:

Geriatric Patient is the Standard Benchmark of Nephrological Care: According to the USRDS (United States Renal Data System), the average age of new ESRD (End-Stage Renal Disease) patient is 62 years. Fifty percent of all patients on hemodialysis are over the age of 65 years. Twenty percent of all ESRD patients are over the age of 75 years. The annual incidence rates of new ESRD patients are shifting from the age group 65-75 years to over 75 years. The risk or modifying factors involve - male gender, hypertension, diabetes mellitus, and dietary and pharmacological factors.

Age-related Changes in the Kidney: Recently, Denic and associates comprehensively reviewed structural and functional changes that occur in aging kidney (12). So, here we only provide a concise report of those changes and their clinical significance. These structural and functional changes are expected to occur in an otherwise healthy individual. Presence of comorbid conditions, such as diabetes mellitus or hypertension, can markedly affect the structural and functional changes and their velocity of occurrence.

Structural Changes: Age-related anatomic changes that occur in the kidney are: (i) decreased kidney size – cortex shrinks more than medulla; (ii) increased glomerulosclerosis; (iii) tubulointerstitial changes, such as decreased number of cells, thickening of basement membrane, increased tubular diverticula, and expansion of interstitium; and (iv) vascular changes – altered vascular pattern, atherosclerotic changes, altered arteriole-glomerular flow (shunt formation). While the kidney mass

shrinks due to micro-anatomical changes such as nephrosclerosis (arteriosclerosis, glomerulosclerosis, tubular atrophy and interstitial fibrosis), there is compensatory hypertrophy of remaining nephrons to preserve kidney function.

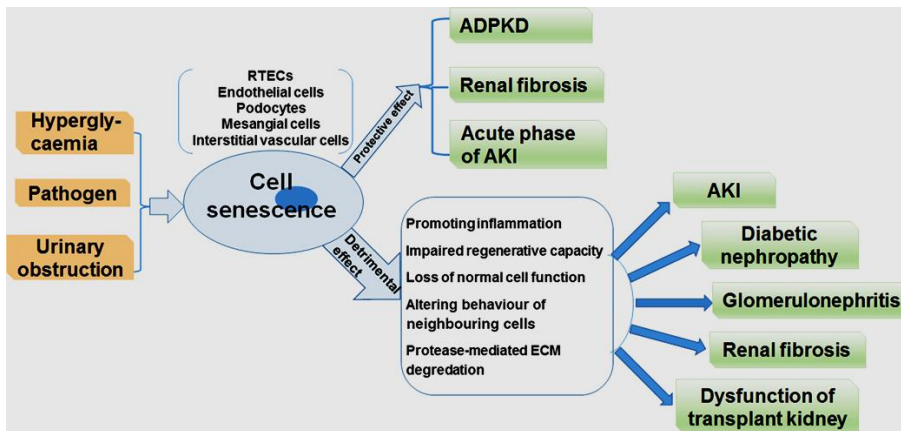
Age-related Functional Changes in the Kidney: The prominent functional changes are: (i) decreased renal blood flow (RBF); (ii) decreased glomerular filtration rate (GFR) – a fall in GFR at 6.3 ml/min/1.73 m² per decade is often seen in healthy kidney donors, and is considered normal age-related decline in GFR; (iii) altered tubular function – impairment in water handling, sodium absorption, acid-base transport, and reabsorption of glucose; and (iv) altered endocrine function – alterations in renin-angiotensin system (RAS), vitamin D metabolism, and response to anti-diuretic hormone. Interestingly the Baltimore Longitudinal Study of Aging showed that one third of the subjects experienced no decline in renal function with age (13).

Clinical Significance of Age-related Decline in Kidney Function: Even in healthy adults, kidney function decreases steadily starting from the age 40 years. However, the rate of decline among different healthy individuals may not be the same. So, there is no such thing as one-size fits all model to assess whether declining kidney function in an elderly patient is physiological or pathophysiological that needs intervention. Yet, there are two things to be remembered. First, a fall in estimated GFR (eGFR) with advancing age is expected, and one should be cautious to avoid misdiagnosing chronic kidney disease (CKD) in elderly patients without a comprehensive evaluation and

laboratory tests. Second, serum creatinine levels in elderly patients are not reliable indicators of kidney function, as blood levels of creatinine reflect skeletal muscle mass. With age-dependent decrease in muscle mass, serum creatinine levels in the elderly can be low even in the face of declining kidney function. The lowest risk of mortality is at eGFR of ≥ 75 ml/min/1.73 m² for age < 55 years. The lowest risk shifts to eGFR values of 45-104 ml/min/1.73 m² for age > 65 years (12). These values allow clinicians to define chronic kidney disease in elderly patients in the absence of other signs of kidney damage. Change in eGFR over time is a more reliable indicator of declining kidney function than snapshot values on one or two occasions. However, among otherwise comparable individuals, the rate of age-related decline in renal function can be different. These

factors highlight the need for dose adjustment of water-soluble medications cleared through kidneys, and for exercising caution with non-steroidal anti-inflammatory drugs (NSAID) and contrast agents in elderly patients. While chronic kidney disease might be an inevitable consequence of aging in many patients, the decreasing functional nephron mass depletes the reserve capacity of the kidney, thus making elderly patients susceptible to acute kidney injury (AKI) at times of illness as compared to patients of younger age with better renal functional capacity. This is exemplified in a recent report of meta-analysis of 79 research articles, showing that age ≥ 60 years and severe COVID-19 as independent risk factors for acute kidney injury (14).

Fig 2: A Schematic View of the Effects of Cellular Senescence in Renal Diseases.



Renal diseases are associated with cellular senescence involving various cell types. In certain renal diseases, such as autosomal dominant polycystic kidney disease (ADPKD), cellular senescence may offer protection. But in other renal diseases, such as acute kidney injury (AKI), diabetic nephropathy, glomerulonephritis and fibrosis and dysfunction following renal transplant, cellular senescence promotes progression of the disease condition. Reproduced from Zhou et al, 2019 (ref # 15; Open Source: Creative Commons Attribution License)

Role of Cellular Senescence in Renal Diseases: Cellular senescence is an emerging field of research with a potential for therapeutic drug development to slow down organ aging and to prevent or counter diseases associated with aging process. Cellular senescence is a state of irreversible cell cycle arrest during cell division. Biologically, it plays a role in embryogenesis, tissue regeneration and repair, aging and prevention of tumors etc. Pathophysiologically, cellular senescence is involved in cardiovascular, renal, and liver diseases through SASP (Senescence-associated Secretory Phenotype) (15, 16). By the secretion of SASP, proteins, senescent cells can influence the surrounding cells in a paracrine fashion. Thus,

senescent cells can exert either beneficial or harmful effects through SASP (Fig 2). Similarly, during the progression of kidney diseases, different cells secrete many factors, which are called CASP (CKD-associated Secretory Phenotype), which share similarities with SASP. The CASP are mediators of crosstalk between cellular senescence and CKD (17). Clinical trials are undergoing on senolytics, SASP inhibitors and nutrient signaling regulators as an approach to promote healthy aging (15, 16). Senolytics are agents that selectively induce apoptosis of senescent cells. Table 1 gives list of current and completed clinical trials on senolytics, SASP inhibitors and nutrient signaling regulators.

Table 1: Clinical Trials of Drugs Promoting Healthy Aging

Drug	Participants and sample size, n	Dose	Duration	Status	Main findings (completed) or research purposes (recruiting)	Reference (completed) or NCT number (recruiting)
Dasatinib plus Quercetin	Patients with IPF, n=14	Dasatinib:100 mg/day, Quercetin:1250 mg/day, three-days/week	3 weeks	completed	Dasatinib plus Quercetin may alleviate physical dysfunction in IPF	Justice <i>et al.</i> , ⁶ USA
Dasatinib plus Quercetin	Adults aged 50–80years with diabetes mellitus and CKD were included, n=9	Dasatinib: 100 mg daily, Quercetin:1000 mg total daily (500mg twice daily)	3 days	completed	Dasatinib plus Quercetin treatment significantly decreased senescent cell burden in humans.	Hickson <i>et al.</i> , ³¹ USA
Dasatinib plus Quercetin	Allogeneic HSCT patients surviving ≥1 year post-HSCT, n=10	Quercetin: 1000 mg daily, Dasatinib:100 mg daily	3 consecutive days	recruiting	Evaluate the biologic markers of premature aging and senescence in HSCT survivors and their correlation with clinical outcomes	[ClinicalTrials.gov identifier: NCT02652052]
Dasatinib	Patients with SSc-ILD, n=12	Not provided	169 days	completed	A decrease in skin expression of SASP and other senescence-related gene sets was associated with Dasatinib treatment	Martyanov <i>et al.</i> , ¹⁹⁶ USA
curcumin	Healthy adults aged 60–85years old, n=60	80 mg per day or per time	Acute (1 and 3h after a single dose), chronic (4 weeks)	completed	Acute: trend in improvement in sustained attention ($p=0.168$) and significant improvement in working memory; chronic: significant improvement in working memory	Cox <i>et al.</i> , ¹⁹⁸ Australia
MitoQ	Healthy older adults (60–79years) with impaired endothelial function, n=20	20 mg/day	6 weeks	completed	MitoQ and other therapeutic strategies targeting mitochondrial reactive oxygen species may hold promise for treating age-related vascular dysfunction.	Rossman <i>et al.</i> , ⁴³ USA
Fisetin	Adults aged 70years or older, n=40	20 mg/kg/day	2 consecutive days	recruiting	Evaluate markers of frailty and markers of inflammation, insulin resistance, and bone resorption while maintaining bone formation in older adults.	[ClinicalTrials.gov identifier: NCT03675724]
Fisetin	Patients with osteoarthritis aged 40–80, n=72	20 mg/kg per day	Orally for two consecutive days, followed by 28 days off, then 2 more consecutive days.	recruiting	To determine whether fisetin reduces senescent cells, pro-inflammatory and cartilage degenerating SASP markers, and reduces osteoarthritis-symptoms leading to improved joint health and function.	[ClinicalTrials.gov identifier: NCT04210986]
Metformin	Patients aged 60years or older, with stable coronary artery disease and prediabetes disease, n=12	500 mg tablet by mouth, every 6–8 h per day	1 years	recruiting	Enhance understanding of the regenerative impact of metformin and the basis for clinical improvement in the setting of senescence.	[ClinicalTrials.gov identifier: NCT03451006]
Rapamycin	Participants more than 40years of age and had no history of diabetes/hypercholesterolemia, n=36	Topical application of 0.5cc rapamycin cream (10 μ M) to the dorsal side of each hand	8 months	completed	Rapamycin reduced the markers of aging and clinical improvement in skin appearance was noted	Chung <i>et al.</i> , ¹⁹⁷ USA

CKD, chronic kidney disease; HSCT, hematopoietic stem cell transplant; IPF, idiopathic pulmonary fibrosis; SASP, senescence-associated secretory phenotype; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

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Role of Dietary and Pharmacological Factors in Aging Kidney:

High Protein Diet: The United States Department of Agriculture (USDA) Recommended Dietary Allowance (RDA) for protein is 0.8 g/kg body weight. But average consumption of protein in the United States is 1.6-fold higher than RDA. At least 50% of Americans consume 2-fold higher than the RDA. Using animal models, in 1980s the group of Barry Brenner demonstrated that

consumption of high protein in the diet causes hyperfiltration in nephrons, leading to glomerular injury and loss of function, and restriction of dietary protein in setting of reduced renal mass can afford considerable long-term protection of glomeruli (18, 19). This opened an avenue for low-protein diet for conservative management of CKD (20, 21). More recently, it has been reported that Mediterranean diet as the diet of choice for patients with CKD (22). Another review suggested that reducing animal

protein and egg yolk and increasing intake of fruits, vegetables and fiber may prevent or delay end-stage renal disease (23). Observational studies from China and Singapore suggested that compared with protein from plant sources, animal proteins may pose increased risk for progression of CKD to ESRD. This difference can be attributable to higher acid and phosphate content of animal protein, and their ability to cause dysbiosis of gut microbiota and inflammation (24). Although the above findings are related to progression of CKD, one cannot rule out the possibility that similar cascade of events in the kidney due to high protein diet in healthy individuals may lead to *de novo* CKD. This is an important issue to be given that high-protein diets are becoming popular for weight loss and control of type 2 diabetes mellitus. Such protein diets may lead to progression of kidney disease, especially in diabetic subjects. These and other issues related to the effect of high-protein diets on kidney health and longevity have been reviewed by others (25, 26). It is known that dietary restriction delays aging process in many species. Recently, it has been shown that dietary restriction of methionine not only delays aging, but also offers renoprotection and prevents muscle weakness in aged mice (27, 28). These studies suggest that renal methionine metabolism and the trans-sulfuration pathway can be a potential target for preventing kidney aging and thus promoting healthy aging. Finally, although studies on CKD patients have shown that protein intake of about 0.8 g/kg body weight can lower the risk, however, epidemiological data suggest that long-term intake of such lower amounts of protein may increase mortality apparently due to a J-curve relationship (29).

Potentially Nephrotoxic Drugs: Elderly people account for 25% of the multi-billion dollar drug market in the USA. The pharmacokinetics and pharmacodynamics of drugs are altered in the elderly, due to reduced functions of both liver and kidney. Many drugs are converted into their active forms or metabolized to inactive forms in the liver, and then excreted mostly through the kidney. Reduced functions of liver or kidney can accumulate toxic levels of drugs or their metabolites in the system. Thus, it is not a wonder that elderly patients account for 40% of all drug toxicities, although they constitute only 12% of the US population. Despite these numbers, several areas of uncertainty remain to be clarified, such as impact of nephrotoxicity of drugs on patient outcomes, the reliability of the available methods for diagnosing an impending acute kidney injury (see below), and the

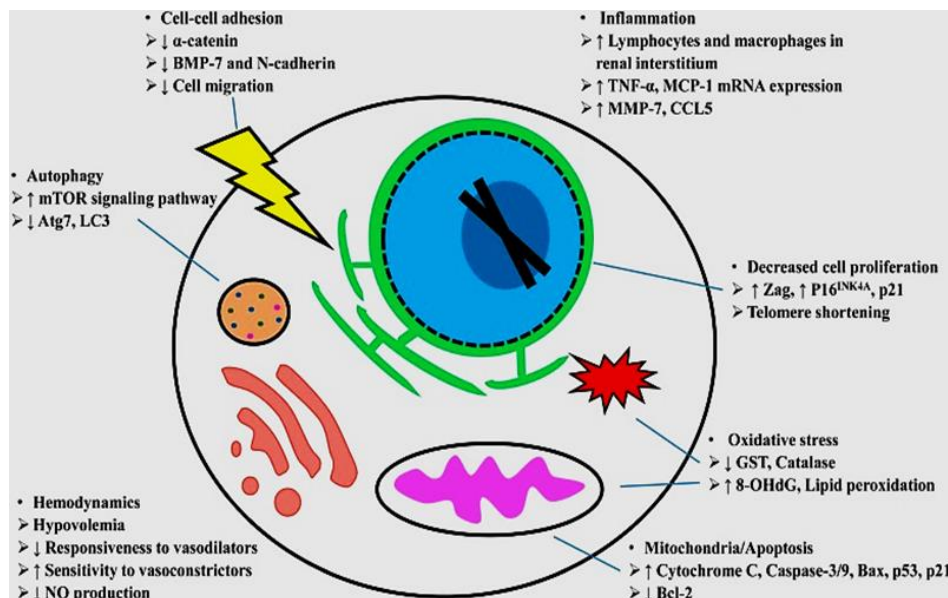
availability or lack of dependable biomarkers. These and other issues are reviewed recently (30).

Medication-induced Acute Kidney Injury in Older Patients: Compared to adults, elderly patients are more prone to develop acute kidney injury (AKI) following simple insults or injuries or acute illness. This is because, the elderly patients have not only reduced renal function, but also low adaptability due to decreased reserve capacity. Acute kidney injury (AKI), previously known as acute renal failure (ARF), is a common clinical condition that affects 4 to 7% of hospitalized patients and often requires treatment in an intensive care unit (ICU). Clinically, it is defined as abrupt loss of renal function, ranging from minor loss to failure. Despite dialysis therapy, AKI has unacceptably high mortality rate ranging from 20 to 35% over 90 days period. Both prevalence and mortality of AKI are higher in elderly patients (31, 32). There are several alterations in aging kidney, that may increase its susceptibility to injury, such as hemodynamics, oxidative stress, apoptosis, autophagy, inflammation, and decreased repair capacity. These have been reviewed by Wang et al (33). Figure 3 illustrates mechanism of increased AKI with aging.

Diseases that Commonly Affect the Aging Kidney: Several diseases commonly affect the aging kidney. These are: (i) Systemic diseases: hypertension, diabetes mellitus, atherosclerosis and dyslipidemia, amyloidosis, light chain deposition, and vasculitis; (ii) Different types of glomerular diseases; (iii) Acute kidney injury due to hypovolemia, septic shock, nephrotoxins, antibiotics, diuretics, contrast media, and chemotherapeutic drugs; (iv) Interstitial nephritis due to non-steroidal anti-inflammatory drugs; (v) Obstructive uropathy – benign and malignant causes; (vi) Renal tumors – primary and metastatic; and (vii) Renal cysts – autosomal dominant polycystic kidney disease (ADPKD).

Age-related Defects in Water and Sodium Homeostasis: Elderly subjects experience deranged homeostasis of water, electrolytes and acid-base due to alterations in renal structure, function and response to hormones and paracrine and autocrine agents. We and others have reviewed basic aspects of deranged homeostasis in elderly subjects extensively (34-37). Of these, the most common ones are deranged homeostasis of water and sodium, which pose considerable clinical challenge, often associated with morbidity or even mortality in high-risk patients. Hence, here we summarize age-related defects in water and sodium homeostasis.

Fig 3: Mechanisms of Increased Incidence of AKI with Aging.



Altered hemodynamics in aging kidney due to conditions such hypovolemia, are common in elderly, setting off vascular responses and decreased nitric oxide production. Decreased antioxidants and increased oxidative stress also play a role in susceptibility to ischemia-reperfusion injury. Mitochondrial dysfunction associated with increased apoptosis in aging kidney predisposes to AKI. Decreased autophagic response in aging kidney prevents the ability to recycle organelles damaged due to AKI. Aging is associated with chronic inflammation resulting in accumulation of lymphocytes, macrophages, and inflammatory cytokines in interstitium. These suppress anti-aging hormone Klotho through the transcription factor NF- κ B-dependent manner. Several factors in the aging kidney inhibit cell proliferation, thus impairing repair capability needed to recover from AKI. In addition, alterations in cell adhesion molecules hamper repair process. Thus, the susceptibility of aging kidney to AKI is multifactorial. Reproduced from Wang et al, 2014 (ref # 33; Open Access: Creative Common CC BY license).

Defects in Water Homeostasis: It has been reported several decades ago that the hypothalamic-neurohypophyseal-renal axis is deranged in elderly subjects. The defects are at various levels, such as (i) altered sensitivity of osmoreceptors and baroreceptors in aging, because of which elderly subjects do not experience thirst response even when dehydrated. (ii) impaired ability to synthesize, store and release arginine vasopressin (AVP) even during conditions of dehydration; (iii) impaired ability of the kidney to respond to circulating levels of AVP and thus concentrate urine; (iv) impaired ability to excrete a load of water; and (v) impaired ability to conserve solutes. Due to the above, the elderly subjects are more prone to develop severe water and electrolyte disorders during episodes of acute or chronic illness.

Many conditions can affect the urinary concentrating ability in elderly patients. These are: ischemic nephropathy; interstitial nephritis; obstructive renal diseases; potassium deficiency; hypercalcemia; diabetes mellitus; congestive heart failure; hypothyroidism; SIADH (Syndrome of Inappropriate Anti-Diuretic Hormone Secretion); Systemic

infections; drugs that inhibit vasopressin release, such as carbamazepine, morphine, promethazine, haloperidol, cisplatin, glucocorticoids, alcohol; drugs that inhibit vasopressin action, such as lithium, demeclocycline, colchicine, glyburide, cisplatin. Drugs that increase vasopressin release, such as nicotine, vincristine, and cyclophosphamide. Drugs that potentiate vasopressin action, such as chlorpropamide; tolbutamide, NSAIDs. While most drug interactions in elderly may have adverse outcomes, a few may be beneficial. Recently, we showed that thienopyridine group of anti-thrombotic drugs (clopidogrel bisulfate and prasugrel) increase vasopressin levels and sensitize renal collecting ducts to the action of vasopressin, thus ameliorate polyuria associated with drugs like lithium (38, 39).

Defects in Sodium Homeostasis: Dysnatremias, both hypo- and hyper-, continue to be the major electrolyte disorders in elderly posing significant challenges in the clinic in terms of diagnosis and management. This is because of a few factors operating in elderly patients. First, with aging muscle mass shrinks and fat accumulates, resulting in a decrease in total body water. Second, aging

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is associated with changes in intracellular volume. Third, hormonal levels, especially those of renin-angiotensin aldosterone, are decreased in aged people. Fourth, renal response to hormones is often blunted resulting in altered handling of sodium by the kidney. Fifth, multiple prescription drugs (polypharmacy) often seen in elderly patients play a role in altered sodium homeostasis. Compounding these are patient-related factors, such as inability to get to a water source, increase in insensible loss of water, and decreased thirst mechanism. Because of these, age is an independent risk factor for developing both hyponatremia and hypernatremia (40). Although most elderly subjects appear to do well, however, a short illness can precipitate severe dysnatremias in them. Mortality associated with hypernatremia in elderly is unrelated to the severity of the condition per se, but it is related to the underlying disease process; it can be as high as 40%. Similarly, presence of hyponatremia complicates any disease and increases mortality in elderly, acting as an

independent risk factor for death. The prevalence of hyponatremia in elderly varies from 2.5 to 50%, depending on whether they live in nursing homes, community dwelling or hospital.

Disclosure: In the past the author received research funding from and collaborated with AstraZeneca and worked on effect of anti-thrombotic drugs on the kidney. Author is an inventor on multiple patents to induce native erythropoietin in the kidney, kidney diseases and obesity, and is a Co-Founder, President, Chief Executive Officer and Chief Scientific Officer of ePurines, Inc., a drug development startup focused on purinergic signaling based therapies for obesity, metabolic syndrome, and kidney and liver diseases. Author declares this review article has been prepared with no industry or commercial support, but in the capacity of Adjunct Faculty at the University of Utah Health.

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Narrative Review

Antimicrobial Associated Harm and the Role for Effective Antimicrobial Stewardship

Vineet Lamba, M.D., and Ramasubbareddy Dhanireddy, M.D.

Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

Edited by:
Kusum Punjabi, M.D., MBA

Reviewed by:
Amandeep K. Pall, M.D.
RWJ Barnabas Health
North Brunswick, NJ

Bharati Deka, M.D.
Robert Wood Johnson Univ. Hospital
Somerset, NJ

Correspondence:
vlamba1@uthsc.edu
rdhanire@uthsc.edu

Received: February 21, 2021

Accepted: April 21, 2021

Citation:
Lamba and Dhanireddy
JAAPI 1(1):76-81, 2021

Importance: Antimicrobial resistance is an emerging global public health concern due to the overuse and misuse of antibiotics. Antimicrobial stewardship is one strategy by which all physicians and healthcare workers can implement change and help curb resistance. Effective stewardship also has the potential to have a tangible improvement in clinical patient outcomes.

Observations: While a lot of the antimicrobial stewardship literature has shown improvement in process measures such as antibiotic usage and its net effect on decreasing resistance, it is still largely perceived as a measure for the “greater good”, rather than being beneficial to the individual patient. There is a relative lack of literature on the direct harm posed by antimicrobials and the long-term consequences of their misuse. Recognizing this direct harm and the role effective stewardship can play in reducing it, may help with wider adoption of antimicrobial stewardship efforts.

Conclusions and Relevance: There is clear evidence for direct antimicrobial associated harm to the patients in the form of poorer outcomes, drug toxicity and in some instance long term health consequence. These harms can potentially be mitigated with effective antimicrobial stewardship.

Abstract:

Introduction: Human exposure to antimicrobials is at a historic high point, due, not only to their medical use, but also due to their utilization in farm animals and crops. This has led to the growing rise of antimicrobial resistance, which is now a global public health challenge. Antimicrobial stewardship programs (ASPs) are one proposed means of curbing misuse in the medical setting and potentially blunting this threat. Several ASP models exist. Thus far, the focus has been on reduction in antimicrobial resistance in general, not the direct benefit to the individual patient. This may in part explain the lack of consistent adherence to these programs. Effective ASPs are important not only in stemming the rise of antimicrobial resistance but also improving quality of care and individual patient outcomes.

Evolution of the Response to Antimicrobial Resistance: The clinical application of antibiotics has been

perhaps one of the greatest medical advances of the 20th century (1). However, misuse of this valuable resource has resulted in the rapid rise of antimicrobial resistance (AMR). Alexander Fleming himself recognized this phenomenon in his 1945 Nobel Prize acceptance speech when he lamented the waning efficacy of penicillin due to its overuse (2). In the past 75 years since then, several multi-drug resistant species have evolved and today AMR is recognized as a global problem. This evolving threat has been met with responses of varying efficacy from global infectious-disease professional organizations. The Centers for Disease Control and Prevention (CDC) in the United States started its first educational efforts to promote optimal use of antibiotics in acute-care hospitals in 2009, and in 2013, the agency highlighted the need to improve antibiotic use as one of four key strategies required to address the growing antibiotic resistance in the United States (3). There has also been a renewed investment in AMR surveillance by the

CDC and the World Health Organization (WHO) as means to monitor for improvement to these interventions (4). While concerted global effort is important, a key component improving antibiotic use has been physician-lead ASPs. In January 2017, this was emphasized in recommendations by the Joint Commission and Centers for Medicare & Medicaid Services (CMS) calling for all hospitals to have stewardship programs (5).

Antimicrobial-Associated Harm: While the focus of ASP has been predominantly to reduce inappropriate antimicrobial use to decrease AMR, a significant hurdle has been the attitude amongst both medical professionals and the public that, for the individual patient, antimicrobial benefit may outweigh potential harm. Accumulating evidence shows that there is harm caused to individual patients by unnecessary or unduly prolonged antimicrobial use. This has long-term ramifications, especially in the pediatric practice (6); this should inform practice for any ASP.

Evidence of Antimicrobial-Associated Harm

Increased Mortality: There is evidence of increased mortality with both unnecessary administration as well as prolonged use of antimicrobials. While the current sepsis guidelines, which emphasize the importance of timely, empirical, broad spectrum antimicrobial therapy, have led to a definite mortality benefit (6-8), they have also led to instances of indiscriminate use of broad-spectrum antimicrobials in patients with uncomplicated infections (9). There is some evidence that early empiric administration of antimicrobials in hospitalized patients, who can be safely monitored without antimicrobials, may cause harm as evidenced by a study by Hranjec et al (10). This study showed a conservative strategy based on waiting for microbiological evidence of infection was associated with lower all-cause mortality (13/100 [13%] vs 27/101 [27%]; $p=0.015$) compared to standard care. Similarly, safely reducing duration of antimicrobial exposure has also been shown to have a mortality benefit. The largest randomized control trial (RCT) studying the utility of procalcitonin guided antimicrobial therapy, showed lower overall antimicrobial use and mortality (11).

A similar phenomenon has been demonstrated in the pediatric population where there is overwhelming evidence of multidrug resistant infection associated mortality in patients ranging from neonates to older children receiving routine empiric antibiotics (12-15). In fact, even in the most vulnerable population of preterm neonates, there is a concern for undue increase in mortality asso-

ciated with early empiric antibiotic use prompting the ongoing NICU Antibiotics and Outcomes Trial (NANO) trial (16).

Increased Risk of Infections: Excessive antimicrobial use has been shown to be associated with increased risk of other infections and the need for hospital admission. An RCT studying community acquired pneumonia treatment duration showed a significant increase in readmission in those treated for longer duration with no significant difference in mortality (17). This is especially apparent in the relatively immunocompromised pediatric population. In extremely low birth weight infants, prolonged initial empirical antibiotic treatment has been associated with increased rates of necrotizing enterocolitis and death (18).

Drug Toxicity: Adverse consequences associated with antibiotic use also extend to direct drug toxicity as evidenced from evaluation of pediatric data from the National Electronic Injury Surveillance System in the United States. Between 2011 and 2015, antibiotic-associated adverse drug events accounted for almost 50% of emergency department visits for adverse events from systemic medications (19). Similarly in a cohort of 1488 adult patients, 20% patients were shown to experience at least one antibiotic-associated adverse drug event (20).

Long-Term Health Outcomes: The impact of early antimicrobial exposure on childhood health outcomes is an evolving area of research. There is evidence to suggest that neonatal antibiotic exposure leads to perturbations in growth (21-23), development of allergic disorders (24), type 2 diabetes (25) and inflammatory bowel disease (26). In multiple cohort studies, antibiotic exposure early in life has been associated with increased risk of childhood obesity and adiposity (21, 22) which may place them at increased risk of early cardiovascular disease (27). In one study, administration of antibiotics within the first year was associated with increased risk of lifetime development of asthma (Odds Ratio (OR) 2.66; CI 1.11-6.40) (24).

Mechanisms of Antimicrobial-Associated Harm

Mitochondrial and Immune Dysfunction: Many patients are treated with antimicrobials for prolonged duration with no clinical or laboratory evidence of infection. Exposure to antimicrobials has been shown to impair mitochondrial function, not dissimilar to what is seen in patients with sepsis, and lead to oxidative damage in mammalian cells (28, 29). Several antimicrobials including ciprofloxacin and ampicillin inhibit the electron transport chain, leading to

excess reactive oxygen species production, DNA damage, worsening of mitochondrial dysfunction, and cellular dysfunction (29). At higher dosing ranges, some antimicrobials are also able to inhibit mitochondrial oxidative phosphorylation (30). Antimicrobials associated cellular dysfunction may explain increased risk of mortality reported in patients treated with antimicrobials for prolonged duration with no clinical or laboratory evidence of infection.

Antimicrobial Resistance: Antimicrobial resistance (AMR) is a well-known antimicrobial-associated harm. While the global increase in the burden of AMR remains a concern (4), for the individual patient, the role of excessive antimicrobial therapy in developing subsequent multi-drug resistant (MDR) infections is frequently overlooked. Infections caused by MDR pathogens are associated with increased mortality and length of stay (31). MDR pathogens are a common cause of ICU-acquired infections in pediatric (32) and adult (33) patients alike. Outside the hospital setting, they are a steadily increasing cause of community acquired pneumonias and community-onset bloodstream infections (34, 35).

Alteration in the Microbiome: Perhaps the fastest growing area of research, is the role of antimicrobials in the evolution of dysbiosis (imbalance of commensal and pathogenic bacteria) in the human microbiome. Significant loss of gut microbiome diversity has been observed in patients exposed to broad-spectrum antimicrobials (36). There is also a trend towards relative abundance of selectively resistant populations. This dysbiosis is associated with an increased risk for local and systemic disease including healthcare-acquired infection (HAI) (37). Alteration of the microbiome also has the potential to confer antimicrobial resistance genes and lead to development of MDR organisms such as the ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and Enterobacter species) organisms (38, 29). The loss of microbial diversity may also drive inflammation and immune dysfunction (40). In the pediatric population, antimicrobial treatment has been shown to alter the microbial balance not only amongst bacteria but viruses and fungi as well (41-43). Normal host-microbiome interaction is key to functioning of the host intestinal and systemic immune response, the exact mechanisms of which are outside the scope of this review but are implicated in the long term complications of obesity, allergic disorder and autoimmune conditions as described previously.

Reducing Harm: The Role of Antimicrobial Stewardship:

Antimicrobial stewardship is clearly a well-recognized area of importance in public health (5). Though, it is often perceived as benefiting the “greater good”, by rationing precious resources and curbing cost, rather than providing immediately palpable benefit to an individual patient. With this review of the evidence and mechanisms behind direct antimicrobial associated harm, we hope that providers realize that effective ASP can potentially lead to direct improvement in patient outcomes as well.

In a consensus statement by the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society, antibiotic stewardship has been defined as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration (44).” In 2014, the CDC compiled a checklist of “Core Elements of Hospital Antibiotic Stewardship Programs” that included the following: support from leadership for the ASP, including appropriate financial support; an identified physician leader for the ASP; a pharmacist co-leader; support from other relevant stakeholders; specific interventions to improve antibiotic use; pharmacy-driven interventions; recommendations for the diagnosis and treatment of specific syndromes; monitoring antibiotic prescribing and resistance patterns and regularly reporting findings to health care workers; and educating health care workers about resistance and optimal prescribing (45). Since then, there has been a robust implementation of ASPs in a variety of healthcare settings (45-49).

Some proven strategies to improve care involve development of guidelines, post prescription review, use of rapid diagnostic testing and diagnostic stewardship. Development and dissemination of standardized care and guidelines for commonly encountered conditions has been shown to markedly reduce variance and improve compliance to ASPs core ideals (49, 50). Implementing a method or review of prescribing practices, whether that is by placing restrictions on antimicrobial ordering or post-prescription review within 48 hours has also been consistently shown to reduce the antibiotic days of therapy (DOT) per 1000 patient-days (52, 52). Post prescription review allows for tailoring of antibiotics based on culture results or discontinuation if no continued need, without the concern of limiting initial empiric coverage. While

these strategies are largely successful in the inpatient setting, a different toolset must be applied to the outpatient setting. Interventions such as provider and patient education, use of rapid diagnostic testing, educating patients of adverse effects have been shown to be successful.

Traditionally the metrics of these programs have focused on process outcomes such as antibiotic use and antibiotic cost which do not always correlate with clinical improvement in care. Clinical outcomes are typically more challenging to measure than antibiotic use, as they can be difficult to define universally and collect. Although improvement in clinical outcomes following optimization of antibiotic therapy is ideal, attempts at reduction in antibiotic use without worsening clinical outcomes are also acceptable. Examples of clinical outcomes to consider include *Clostridioides difficile* infections (CDI), antibiotic resistance, antibiotic-associated adverse drug events, length of stay, hospital readmission, and mortality.

Reduction of antibiotic resistance attributable to stewardship programs has not been extensively evaluated. When it has, the results have been mixed in both adult and pediatric literature (53-55). Hospital length of stay is frequently studied as a metric in healthcare interventions, though less often for ASPs. In one children's hospital in which post-prescription review and feedback were used, hospital length of stay was reduced by approximately one day, and 30-day readmission rate was reduced by 3% (56). Similarly, in one adult study there was a significant difference in 60-day readmission rate for relapsing

infection (3.4% intervention, 7.9% control, $p=0.01$) (51). Any decrease in mortality has been difficult to associate with ASP interventions; however, multiple studies have shown that rationing of antimicrobials has not led to an increase in mortality (52). In certain populations, such as hospitalized cancer patients with febrile neutropenia, ASP adherence was shown to be independently associated with lower mortality (57).

Future Directions: Most of the measures and evidence described above emanate from developed nations with a relatively mature healthcare infrastructure capable of providing financial and logistical support for ASPs. However, resource-limited nations account for the bulk of global antibiotic consumption (58). ASPs in these settings face unique challenges of unregulated over-the-counter antimicrobial availability, high rates of antibiotic consumption while overall limited access to antibiotics. This requires novel strategies such as prescription monitoring, public health education while implementing measures to improve access in areas of need. Another source of antimicrobial consumption is their use in agriculture. In the United States up to 70% of antimicrobials are utilized in agriculture (59). There is evidence correlating AMR in humans to use in agriculture (60). This is a key area for ASP activities at a national level. National programs to monitor antimicrobial distribution in animals would be essential in mitigating harm of antimicrobial overuse.

Disclosure: The authors declare no competing interests.

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AAPI YPS/MSRF Research Symposium

The Young Physician Section (YPS) and the Medical Student, Resident, and Fellow (MSRF) section of the American Association of Physician of Indian Origin (AAPI) are two distinct groups that work closely to promote educational activities, networking opportunities, and a sense of community within the young AAPI members. The groups coordinate with the Executive Committee and the parent AAPI chapter to provide medical students, residents, fellows, and young physician the platform which educates and provides them with opportunities to present their work including research, and helps them to achieve their goals of becoming better and well-rounded physicians of Indian origin practicing in the United States.

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RESEARCH & POSTER PRESENTATION

YPS/MSRF conduct Winter Medical Conference (WMC) on a yearly basis to promote research activities and social networking amongst the young physicians. This year's virtual WMC allowed for record breaking attendance and participation in educational activities. It was held on February 21, 2021 and was divided into two parts:

Oral pre-recorded presentation followed by live virtual Q&A session.
Live virtual poster presentation.
Judges were provided with submitted abstracts and judging rubric for both parts.

Judges for WMC Research Competition

Oral Presentation:

Dr. Hetal Gore
Dr. Anita Uppal
Dr. Raj Alappan

Poster Presentation:

Dr. Anupama Gotimukula
Dr. Subbarao Bollepalli

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WMC 2021 Research Symposium Winners

Oral Presentation

1st Place: Ms. Virali Shah (\$500)
2nd Place: Dr. Zeeshan Mansuri (\$200)
3rd place: Mr. Dhruv Patel (\$100)
4th place: Mr. Karan Patel (\$50)
5th Place: Dr. Pranav Sharma (\$50)

Poster Presentation

Dr. Chail Shah (\$50)
Dr. Nihal Satyadev (\$50)
Dr. Hridya Harimohan (\$50)
Dr. Sravani Konatham (\$50)
Dr. Pallavi Tatapudy (\$50)

Acknowledgement

This symposium would not have been possible without the hard work of my team members especially Priya Uppal and Nisha Depa (our in-coming PR and Community Service Chair). We would like to thank Dr. Sudhakar Jonnalagadda, President of AAPI, and his entire Executive Committee for their unconditional support.

Thank you

Ami Baxi, M.D.
YPS President

Kinjal Solanki, M.D.
MSRF President

Winning Abstracts

WMC-21-001:

Rate and Predictors of 30-Day-Readmission among Patients with Major Depressive Disorder: A Nationally Representative Study

Zeeshan Mansuri^{1*}, MD, MPH; Chintan Trivedi^{2*}, MD MPH; Abhishek Reddy³, MD; ¹Department of Psychiatry, Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts, USA. ²St. David Medical Center, Austin, Texas, USA. ³Department of Psychiatry, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA

*Dr. Mansuri and Dr. Trivedi share equal credits for first author

Introduction: Major depressive disorder (MDD) related hospitalizations cause a substantial burden on the patient as well as the healthcare system. There is a paucity of studies readmission information among patients with MDD. We sought to evaluate the rate and predictors of 30 days readmission among MDD patients in adults (age 18-64).

Methods: Patients with the index inpatient admission for MDD were obtained from the National readmission dataset (NRD) Jan-Nov 2016. Primary outcome was the rate and predictors of 30-day readmission (RA-30). The t-test, Chi-square test, and logistic regression analysis were performed.

Results: Weighted Data of 250135 adult patients (mean age: 38 years, female: 54%) were included. Rate of 30 days readmission was 8.7% among adults (mean time to RA-30: 12.7 days). MDD was the main cause of RA-30 (50% adults), followed by other mental illness (20% adolescents, 30% adults).

In adult patients with RA-30, there was a high prevalence of personality disorders (14% vs. 11%, $p < 0.001$), psychotic disorders (6% vs. 4%, $p < 0.001$) and substance use disorders (59% vs. 54.0%, $p < 0.001$) compared to those with no readmission. There were more readmissions among male (54% vs. 45%). Slightly more patients had anxiety disorders in RA-30 group (51% vs. 50%, $p: 0.01$).

Conclusion: There is a high rate of readmission among the MDD population mainly because of the higher prevalence of comorbid psychiatric disorders. Addressing these factors may potentially help reduce the readmission rate in this vulnerable population and the associated financial burden on the hospital.

WMC-21-002:

Durvalumab Induced Severe Hypothyroidism in a Patient with Recurrent Squamous Cell Lung Cancer

Chail Shah, MBBS; Jasneet Randhawa, MBBS; Ratesh Killan, MD. KingsBrook Jewish Medical Center, Brooklyn NY, 11203

Background: Immunotherapy is growing its popularity due to fewer side effects and better drug tolerance in cancer management and is replacing chemotherapy. Because these treatments are new and immunotherapy has different side effects, physicians are not very well versed with them. Most of the side effects of immunotherapy are because of cytokine surge hence the treatment is different. We are discussing a case of severe hypothyroidism secondary to durvalumab that is associated with immune-mediated endocrinopathies.

Case Presentation: 70-years old female with a medical history of lung cancer (dx 2015, s/p left upper lobectomy, recurrent poorly differentiated squamous cell carcinoma, left lower lobe, diffusely positive for p40 while negative for TTF-1 in April 2019 s/p chemo and radiotherapy), hyperlipidemia, COPD and hypertension comes to the clinic with swelling of the face, shortness of breath, fatigue and weight gain. The patient was started on durvalumab on 08/2019 for 12 months as per NCCN guidelines for adjuvant treatment of her (T3N0M0) Stage 2b lung cancer after chemotherapy and radiation treatment. Physical examination was positive for abdominal distension, swelling of the face, and bilateral lower extremities, decreased breath sounds in bilateral lower lobes. The patient was started on furosemide 20mg OD and started feeling better for a few days before the symptoms worsened. We checked her thyroid function test as she had symptoms of hypothyroidism, labs showed TSH: >49 , T3:26.9, and T4:0.70. The patient was diagnosed with durvalumab induced severe hypothyroidism and started on 50MG levothyroxine OD. The patient is feeling better after starting levothyroxine and the swelling and symptoms have reduced with TSH trending down. The patient continued taking durvalumab as per NCCN guidelines.

Discussion: This case is a rare side effect of immunotherapy. Treatment involves the replacement of thyroid hormone. It's imperative to check thyroid function tests at least every 3 months while the patient is on durvalumab. Side effect profile of immunotherapy is mostly immune-mediated pneumonitis, colitis, hepatitis, and endocrinopathies. And these side effects are treated with steroids. Whereas chemotherapy mostly causes side effects by

infections due to immunosuppression and treated by antibiotics and GCSF agents.

Conclusion: Our patient with recurrent squamous cell lung cancer developed hypothyroidism secondary to durvalumab.

WMC-21-003:

Radiographic and Health Economic Analysis of Acetabular Retractors Placement Relative to Neurovascular Structure in Total Hip Arthroplasty Surgical Approaches

Author: Dhruv Patel¹, MBA; Shelton S. Schmidt², PhD
¹Albany Medical College, Albany Medical College, Albany, NY, Albany, NY 12208
²Union College

Reports estimate 2.5 million Americans have undergone total hip arthroplasty, the primary treatment for patients with degenerative hip joint disease, and are living with implants. It can significantly improve patients' quality of life and is one of the most commonly performed operations in the United States, especially given the aging population. However, approximately 0.6 - 7.6%, experience femoral nerve palsy as a complication of the procedure and 0.1 - 0.2% experience vascular damage of which 79% were left with some degree of persistent neurologic dysfunction even after additional medical care. These complications in turn often lead to patient readmission, which is of particular interest to hospitals since most face 30-day and 90-day readmissions penalties and also receive less money from Medicare for readmissions. Total hip arthroplasty has several surgical approaches including direct-anterior, direct-lateral, and direct-posterior approaches.

Since retractor placement during surgery is the main cause of this complication, one purpose of this study was to investigate the proximity of the retractors to the femoral nerve during the various approaches to total hip arthroplasty using radiographic measures. By determining the most optimal location for the retractors in total hip arthroplasty and conducting cost analysis of the three surgical approaches to THA, we hoped to develop a plan for physicians to decrease the incidence of femoral nerve palsy and decrease total cost of total hip arthroplasty amongst various high risk demographic groups. Our analysis found the direct-anterior approach to have a shorter hospital length of stay, lower costs in 8 of the 10 categories considered, and the foundation for a possible quicker recovery time.

WMC-21-004:

Concurrent Presentation of A Complex Mixed Auto-immune Encephalitis Subsequent To Mycoplasma Pneu-moniae Infection: A Case Report and Literature Review.

Nihal Satyadev MPH¹, Surpreet Khunkhun B.Sc¹, Yulia Kungurova B.Sc¹, Samir Ruxmohan DO², Kamalpreet Mann MD³, Gabriela Perez DO⁴, Hyder Tamton DO²

¹University of Medicine and Health Sciences, St. Kitts and Nevis, WI ²Larkin Community Hospital, South Miami, Florida, USA ³ Mercy Health Hauenstein Neuroscience Center, Grand Rapids, Michigan, USA ⁴ Palmetto General Hospital, Hialeah, Florida, USA

Background: A PUBMED search was conducted using the keywords "Autoimmune encephalitis" OR "Bickerstaff encephalitis" OR "Miller Fisher" OR ("Paraneoplastic encephalitis" AND "Plasma Exchange"). Common trends in age, gender and the average number of sessions of plasmapheresis or plasma exchange therapy were identified in 178 cases between the years 1981 and 2020.

Aim: To report a unique case report and associated literature review of autoimmune encephalitis in a patient following a Mycoplasma pneumoniae infection.

Case Description: A 40-year-old female with a history of Hashimoto thyroiditis, polycystic ovarian syndrome, and a lower respiratory infection came into the emergency department with new onset, progressive neurological symptoms. These included generalized tonic-clonic seizure and worsening respiratory status that required intubation and tracheostomy. Blood cultures returned positive for Mycoplasma pneumoniae. MRI brain showed several hypointense soft tissue masses within the posterior occipital scalp region. CSF studies were positive for anti-TPO, anti-GAD65, anti-M2, anti-HLA class I, anti-Ib, anti-Ilb/IIla and anti-SSA (Ro) antibodies. The patient was initially treated with two rounds of IVIG therapy. Once autoimmune encephalitis was suspected, pulse steroid therapy was combined with IVIG treatment. Due to minimal improvement plasma exchange therapy was started, after which the patient's symptoms improved. We report a unique mixed diagnosis case of Anti-GAD65, Bickerstaff brainstem encephalitis, Hashimoto's encephalopathy, and Miller Fisher Syndrome concurrently.

Conclusion: Literature review cases identified were 40.3% male and 59.7% female. With 27.3% <18 years old and 72.7% >19 years old. Age of onset ranged from 1 to 79, with a median age of 34.4 years old. Plasma exchange or plasmapheresis therapy was implemented in 69.7% of the cases for an average number of 6.3 sessions. Our case report aims to provide further evidence to support plasma

exchange therapy as an alternate treatment option to IVIG refractory cases of autoimmune encephalitis.

WMC-21-05:

A Specific Coagulation Disorder of Uncommon Cause

Hridya Harimohan (MBBS), Mathew Thomas MD FRCP (Lond) FRCP (Edin) FICP FISHTM, Neeraj Siddharthan Kerala, Institute of Medical Sciences, Kerala, India

Background: Coagulation abnormalities are common in clinical practice. Causes include: 1. Vitamin K deficiency due to a) liver and gall bladder diseases, b) cystic fibrosis, c) intestinal (malabsorption or intake deficiency), d) medications and toxins, e) Vitamin K dependent clotting factor deficiency (VKCFD) (genetic). 2. Antibodies against clotting factors, e.g. factor VIII 3. Disseminated intravascular coagulation.

Case Description: 61-year-old female with hypertension presented with haematuria-1 day. No dysuria. History of epistaxis and melena 2 and 3 days back. No history suggestive of malabsorption or liver/gallbladder disease. No history of any trauma, intake of herbal/alternative medicines or special diet. No past, obstetric and family history significant of bleeding. On examination, conscious and oriented. Vital signs were stable. Systemic examination: Normal. Laboratory investigations showed haemoglobin of 11.9g/dl. Clotting time (29min), prothrombin time (INR 13.3), activated partial thromboplastin (aPTT) (96.9 sec) were elevated. Mixing study showed correction of prothrombin time and activated partial thromboplastin time (aPTT) by normal plasma indicating factor deficiency. Factor assay showed deficiency of vitamin K dependent coagulation factors (II, VII, IX, X). Other factors were normal. Patient was treated with fresh frozen plasma, cryoprecipitate, vitamin K causing partial correction of the coagulation factors. Her bleeding symptoms resolved and is on follow up. INR and aPTT are still out of range.

Conclusion: Common causes of vitamin K deficiency were not present after detailed history, physical examination and investigations. Treatment with vitamin K improved the symptoms but was not able to correct the laboratory findings. A mild genetic defect of VKCFD which was asymptomatic and manifested now at a later stage is also considered. She is now on vitamin K and on follow up and clotting factor assay will be done to determine the cause.

- Complete correction of factors will suggest deficiency of vitamin K due to obscure acquired causes.
 - Partial correction of clotting factors will suggest a mild form of rare hereditary VKCFD. We also plan to do a genetic test in the future (if possible).
- Serum thyroid hormone changes during whole body hyperthermia.

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WMC-21-006:

Assessing Burnout in Physicians: Surgery Versus Medicine

Karan Patel, BS1, Liseth Lavado, BS2, Ank Agarwal, BS3, Sean Bunacthia, BS3, Mohammed Yousif Rashid, MBCHB4, Aaron Lyon, BS5

1. Cooper Medical School of Rowan University, Camden, NJ
 2. Rutgers University School of Nursing, Newark, NJ
 3. Johns Hopkins University, Baltimore, MD
 4. California Institute of Behavioral Neurosciences & Psychology, Fairfield, CA
 5. BYU Idaho, Rexburg, ID
- Email: patelk48@rowan.edu

Background: Physician burnout has been a long-standing problem for the medical community; burnout rates among physicians are the highest of any profession. However, sub-specialties within medicine significantly differ in their burnout rates.

Aim/Hypothesis: We suspected that burnout rates were different between surgeon and non-surgeon physicians. We first tried to show this and then determined what factors cause this difference.

Methods: We performed a systematic review and used data from Medscape's National Physician Burnout and Depression Reports from 2017 to 2020. The data reported by Medscape from various specialties was first split into two categories: medicine and surgery. We then found the average rate of burnout within each group and calculated a p-value and odds ratio. Then, we searched various databases such as PubMed and Google Scholar to determine the top factors related to burnout and compared those between non-surgeon and surgeon physicians.

Results: The average rate of burnout among the top five surgical specialties was 44.7% compared to 49.4% for the top five non-surgical specialties (OR: 1.25; 95%CI: 1.11-1.35; p<0.05). The factors that led to higher burnout rates among non-surgeons physicians vs. surgeon physicians were: increased time spent on the EHR (31.5 hours for non-surgeon physicians vs. 23.7 hours per week for surgeon physicians), extended periods spent on administrative

tasks (3.5 hours for primary care physicians vs. 2.1 hours for surgeons per week), and decreased compensation (\$407,000 for surgeons to \$334,000 for non-surgeon physicians). Subjective measures also showed those in medicine tend to feel less respected compared to those in surgery.

Conclusion: There is a clear difference between burnout rates among physicians in surgery and medicine. Determining the causes for this difference will better allow us to implement solutions to help reduce burnout rates among non-surgeon physicians.

WMC-21-007:

A 33-year-old Woman with Severe Subacute Thyroiditis Post COVID-19

Sravani Konatham MBBS¹, Sai Rohit Reddy Mekala MBBS², Lubna Mirza MD³

¹Kamineni Institute of Medical Sciences, Narketpalli, India.

²Armed Forces Medical College, Pune, India

³ Endocrinology, Norman Regional Health System, Oklahoma, USA.

Background: The novel severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) virus has led to the pandemic of Coronavirus disease 2019 (COVID-19). COVID-19 has wide range of complications; cases of subacute thyroiditis have been reported post COVID-19.

Aim: To highlight the severity of subacute thyroiditis post COVID-19 infection in comparison to other etiologies and timely intervention with high dose steroids and anti-inflammatory drugs.

Case Description: A 33-year-old woman was referred to endocrinology clinic with swelling and pain of her anterior neck for four weeks duration. She developed her symptoms two weeks after contracting COVID-19 viral infection. Initially, she noticed swelling and pain in her neck, which was radiating toward the right ear. She also had a fever with malaise and myalgia. Her primary care physician prescribed medrol dose pack twice but her symptoms resumed as soon as she stopped it.

On physical examination, her temperature, blood pressure and heart rate were normal. She is obese with a BMI of 32. Neck exam revealed thyromegaly and anterior neck tenderness. Laboratory investigation revealed low thyroid-stimulating hormone (TSH) of 0.04mU/L. Free thyroxine (T4) was normal. Thyroid peroxidase antibody and thyroid-stimulating immunoglobulin were negative. Thyroid ultrasound revealed a heterogeneously enlarged thyroid gland with two small 4 mm solid hypoechoic nodules in the isthmus. She was treated with the third round of medrol dose pack but her condition relapsed after

completing it. Our patient was started on oral prednisone 40 mg per day with Ibuprofen 800 mg once daily. Her symptoms improved within two weeks and steroids were tapered off gradually.

Conclusion: Subacute thyroiditis is a self-limiting complication of various viral infections that generally responds well to short course of steroids. Our case highlights the unusual severity of subacute thyroiditis after COVID-19 infection and the role of early aggressive therapy with high dose steroids to limit morbidity.

WMC-21-008:

Transplant Renal Artery Stenosis as a Potential Cause of Early Allograft Failure

Sharma Pranav, MD, Puri Sonika, MD, FASN

Division of Nephrology, Robert Wood Johnson Medical School, New Brunswick, NJ; Email: pranavstanely@gmail.com

Background: Renal artery stenosis is a frequent vascular complication post-transplant. It is well established that early detection and prompt correction leads to lower morbidity and risks of allograft dysfunction. Although noninvasive imaging can detect an underlying stenosis, it is not confirmatory. This makes decision of contrast arteriography challenging in an already failing allograft. However, angiography with subsequent angioplasty with or without stenting, provides definitive diagnosis and treatment.

Case Description: A 69-year old man with past medical history of end stage renal disease on hemodialysis, diabetes type 2, history of right nephrectomy due to Renal cell carcinoma, underwent a deceased donor kidney transplant. His baseline creatinine was near normal on discharge. After three months, patient presented with lower extremity edema with decrease urine output in the setting of uncontrolled hypertension and worsening renal function. A prompt renal artery duplex revealed high resistive indices and significant renal artery stenosis. Subsequently patient underwent a renal angiogram which a high grade (more than 90%) ostial stenosis in the transplant renal artery. Renal angiography followed by stent placement was thereby done that restored patency of the transplant artery and normal blood flow to the kidney. The procedure resulted in optimal blood pressure control, improvement in symptoms and normalization of renal functions after few days.

Conclusion: Advances in diagnostic and device technology have allowed improved diagnosis and percutaneous management of TRAS. Percutaneous transluminal angioplasty with or without intravascular stenting has high technical success with an acceptable complication rate and it could be preferred initial therapy in these patients.

WMC-21-009:

Educational Module on ADHD: Neuroscience Simplified

Pallavi Tatapudy MD¹, Carlos Hallo MD², Chris Karampatsis, MD, MPH, FAPA³

¹ Stony Brook University Hospital, Stony Brook Medicine PGY-1 Psychiatry Resident; ² Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, PGY-1 Psychiatry Resident; ³ Institution Affiliation: NYU Long Island School of Medicine, Adjunct Assistant Professor

Background: While Attention-Deficit/Hyperactivity Disorder (ADHD) neuroscience literature has substantially increased in recent years, the information remains disjointed, fragmented, and difficult to digest. Explaining ADHD in the context of its underlying neurocircuitry may provide the foundation for a new platform to educate trainees, patients, families, and school staff to improve patient outcomes.

Aim: We aim to share a novel conceptualization of ADHD that distills the neuroscience and pathophysiology of

ADHD to basic networks and nuclei – the task-positive, task-negative, and reward networks.

Methods: 48 medical students completed pre-tests, viewed the 19-minute-long evidence-based video module with graphical explanations, and filled out post-tests to assess clinical knowledge, and the perceived value of a neuroscience platform in the understanding of ADHD and comfort in utilizing this information in patient care.

Results: Data analysis revealed that medical students reported the “Educational Module on ADHD: Neuroscience Simplified” as a useful learning tool leading to enhanced absorption of the neurobiological basis of ADHD and increased comfort in using this approach for educational purposes to apply in clinical settings.

Conclusion: Results suggest that our module which correlates the criteria for ADHD outlined in the Diagnostic and Statistical Manual-5 (DSM-5) with the corresponding neurocircuitry in the brain is a valuable learning alternative for medical trainees with the potential to reduce the stigma around ADHD and provide resources resulting in timely diagnosis and appropriate interventions.

All Other Abstracts

WMC-21-010:

Acelofenac Induced Stevens-Johnson Syndrome (SJS) Toxic Epidermal Necrolysis (TEN)

Ram Charan Peddini, M.B.B.S Andhra Medical College, Maharanipecta, Visakhapatnam, Andhra Pradesh, India

Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, potentially life-threatening, severe mucocutaneous adverse reactions characterized by extensive epidermal detachment, erosion of mucosae and severe constitutional symptoms. The incidence of SJS varies from 1.2 to 6/million patient-years and that of TEN being 0.4–1.2/million patient-years, with the mortality rate in TEN being three times higher than that of SJS. High-risk drugs for the development of SJS-TEN include phenobarbital, phenytoin, carbamazepine, lamotrigine, nevirapine, nonsteroidal anti-inflammatory drugs, allopurinol, cotrimoxazole and fluconazole.

Aim: This case outlines the importance of early diagnosis, rapid identification and cessation of the causative drug in addition to supportive care for a better outcome.

Case Description: A 40yr old female patient who was operated for right sided cerebellopontine angle tumour 1 month back presented to OPD with redness and watering

of eyes along with oral mucosal erosions and blisters over face and neck since 2days. On further evaluation the lady mentioned that she had taken tab acefenac which was prescribed by the local doctor for the complaint of surgical site pain. After that she started developing these lesions. A diagnosis of Steven Johnson syndrome was made based on clinical examination and history and was admitted. Immediately the drug was withdrawn and supportive therapy was started. The lesions progressed into toxic epidermal necrolysis spectrum involving >30% BSA. Prognosis was assessed using SCORTEN. Patient was treated in a multidisciplinary approach. Systemic corticosteroids and cyclosporine were the main stay of treatment along with general measures. Finally, the patient was recovered and discharged.

Conclusion: Stevens–Johnson syndrome and toxic epidermal necrolysis are severe, life-threatening mucocutaneous adverse drug reactions with a high morbidity and mortality. The management essentials include early recognition of the condition, cessation of suspected drug(s), supportive therapy, initiation of specific therapy, management of complications and prevention of future episodes.

WMC-21-011:

Morvan's Fibrillary Chorea And Autoimmune Encephalitis Subsequent To Mycoplasma Pneumoniae Infection In A Young Hispanic Female With Rare Autoimmune Antibodies: A Case Report.

Hyder Tamton¹ D.O., Surpreet Khunkhun² B.Sc, Kamalpreet Mann³ M.D., Samir Ruxmohan¹ D.O., Gabriela Perez⁴ D.O., Nihal Satyadev² MPH, Kunal Aggarwal⁵ B.Sc

¹Larkin Community Hospital, South Miami, Florida, USA

²University of Medicine and Health Sciences, St. Kitts and Nevis, WI ³Mercy Health Hauenstein Neuroscience Center, Grand Rapids, Michigan, USA ⁴Palmetto General Hospital, Hialeah, Florida, USA ⁵St. George's University, Grenada, WI

Background: Morvan's syndrome is a rare condition (with male predilection 19:1) that is most commonly associated with thymoma, autoimmune diseases, limbic and paraneoplastic processes. Literature reports cases of Morvan's associated with autoantibodies to voltage-gated potassium channels complexes (VGKCs). However, there are only a few case reports mentioning NMDA as a cause of Morvan's and no reports mentioning AMPA, GABA, and Anti-GAD association with Morvan's.

Aim: To report Morvan's Fibrillary Chorea and autoimmune encephalitis subsequent to Mycoplasma pneumoniae in a young female with CSF positive for VGKC, NMDA, AMPA, GABA, and Anti-GAD65 autoimmune antibodies.

Case Description: We report a young female previously hospitalized due to Mycoplasma pneumoniae infection with MRI brain showing multiple strokes involving the basilar artery and the limbic system, requiring anti-edema therapy, VP shunting and decompressive surgery. She then presented to the emergency department with sudden onset hyperesthesia, spontaneous diffuse muscle twitching predominantly in the left side of her neck, severe restlessness, tachycardia in the absence of fever, sleep disturbances, bilateral pupillary dilation, agrypnia excitata and oneiric stupor. Multiple routine EEGs showed moderate, diffuse encephalopathy, but no epileptiform activity. Anticholinergic delirium, serotonin syndrome and neuroleptic malignant syndrome were ruled out. CSF studies showed positive VGKC, NMDA, AMPA, GABA, Anti-GAD65 autoimmune antibodies. The patient's clinical presentation and lab results both met the criteria for autoimmune encephalitis with concomitant Morvan's syndrome. A five-day course of IV steroids, six day course of IVIG, and subsequently a two week course of Rituximab was initiated, but the patient showed no improvement. Finally, eight sessions of plasma exchange therapy was performed resulting in marked improvement of her neurological symptoms.

Conclusions: To our group's knowledge, we present the first case report of Mycoplasma pneumoniae as an etiology

of autoimmune encephalitis with Morvan's syndrome in a patient with a unique autoimmune antibody profile.

WMC-21-012:

Acute Liver Failure In Postpartum Patient: A Rare Complication Of Dengue Infection

Dr Shilpa Sapre¹; Dr Henil Upadhyay²; Dr Charmy Parikh²

¹Professor, Dept. of Obstetrics & Gynecology, Pramukhswami Medical College, Anand, Gujarat, India.

²Medical Intern, Pramukhswami Medical College, Anand, Gujarat, India.

Background: Dengue fever is a major public health problem in developing countries like India. Symptomatology of dengue ranges from mild self-limiting illness to fulminant liver failure. Hepatic dysfunction is a known complication in dengue fever that ranges from mild to moderate elevation of serum transaminases to catastrophic fulminant liver failure. Acute liver failure is a rare complication of dengue infection with a high mortality rate.

Aim: Successful management of acute liver failure in a case of dengue infection in postpartum patient by multidisciplinary approach.

Case Description: We report a case of 19-year-old female who was referred for management of primary postpartum haemorrhage with acute febrile illness. Laboratory investigations revealed anaemia, thrombocytopenia and positive dengue NS1 antigen test. Patient was managed in critical care unit for pulmonary oedema, acute kidney injury and deranged coagulation profile secondary to hepatic dysfunction. Postpartum haemorrhage was another challenge tackled conservatively. Spectrum of liver involvement varied from a modest rise in transaminases in the early phase and culminating finally in acute hepatic failure by the end of second week. Multiple blood and blood products were transfused during her one month admission in intensive care. There was no perinatal transmission. Multidisciplinary approach involving obstetricians, intensivists and gastroenterologist resulted in successful recovery of the patient from acute liver failure.

Conclusion: Clinicians should have a high index of suspicion for dengue fever in endemic areas in a case of Acute Febrile Illness with/without the classical signs and symptoms of dengue fever. Pregnancy poses a special challenge for the obstetrician as delivery during this period can have devastating complications. Multidisciplinary approach with cautious fluid management is advisable in patients with severe dengue infection. Acute liver failure is a rare complication but can develop in patients with severe hepatitis. Dengue infection in pregnancy can mimic other causes of thrombocytopenia like HELLP syndrome,

megaloblastic anaemia and gestational thrombocytopenia hence a detailed evaluation is warranted in pregnant women presenting with acute febrile illness with thrombocytopenia.

WMC-21-013:

A Study to Assess the Level of Burnout and its Determinants Among Medical Practitioners Working in Tertiary Care Hospital in South India

Niharika Bheemisetty MBBS¹, G.Ananda Krishna MD², C. Chandra Sekhar MD³

¹KS Multi-Specialty Hospital, Hyderabad, India

²Osmania Medical College, Hyderabad, India

³Apollo Institute of Medical Sciences and Research, Chittoor, India

Background: Burnout is defined as “a state of physical, emotional, and mental exhaustion to working conditions that are stressful, demanding, and lack of recognition.” High patient load, long working hours, and unreasonable demands from patients make medical practitioners vulnerable for stress and burnout.

Aim: The objective was to study the prevalence of burnout among medical practitioners and factors associated with burnout.

Materials and Methods: The study is an observational descriptive cross-sectional study conducted among medical practitioners in a tertiary care hospital. The sample studied 102. Study was conducted using the Maslach Burnout Inventory with additional questions on demographic factors, work experience, hours of work, and specialty. Data was entered in MS Excel 2007 and analyzed with SPSS 21 version software.

Results: About 26 (25.5%) members are suffering from burnout in any one of the three dimensions. Out of 102 subjects, it is found that in emotional exhaustion, 15 (14.7%) are experiencing high burnout, 14 (13.7%) members and 73 (71.6%) members are experiencing moderate and low levels of burnout respectively. But in the depersonalization dimension, just 1 (1%) member is experiencing high burnout whereas 11 (10.8%) members and 90 (88.2%) members are having moderate and low levels of burnout respectively. In the personal accomplishment dimension, 16 (15.7%) members revealed that they have high burnout, whereas 13 (12.7%) members and 73 (71.6%) members have shown that they have moderate and low levels of burnout respectively.

Conclusions: Burnout exists among medical practitioners, and measures should be taken to identify causes and take remedial actions.

WMC-21-014:

When the Wall Quivers: Isolated Atrial Septal Aneurysm and Cryptogenic Stroke

Manasa Jasti MD1, Prachi Jain MD1, Natalie Tapaskar MD1, Komal Kaul MD1 1Department of Internal Medicine, Loyola Medicine - MacNeal Hospital, Berwyn, IL

Background: Atrial septal aneurysm (ASA) is usually detected incidentally on echocardiogram. ASA is mobile interatrial septum in the region of fossa ovalis. Literature shows higher prevalence of ASA in patients who present with cryptogenic stroke, especially in age <55 years. ASA is commonly associated with intra-cardiac shunts like patent foramen ovale (PFO), atrial septal defect (ASD) and hence, paradoxical embolism can occur. However, cryptogenic stroke in the setting of isolated ASA is rare.

Aim: We present and discuss a unique case of cryptogenic stroke in the setting of isolated ASA.

Case Description: A 50-year-old gentleman with history of well-controlled depression presented to emergency department with left upper extremity and left-sided facial numbness and paresthesias for one week. Physical examination was notable for decreased sensation of left-sided face and left upper extremity. Workup including complete blood count, thyroid studies, antinuclear antibodies, coagulation studies and lipid panel was unremarkable. CT head showed focal lucency in the right parietal region. MRI of brain showed late subacute infarction in the right parietal region. Transthoracic and transesophageal echocardiogram were notable for a highly mobile atrial septum, consistent with atrial septal aneurysm, with no evidence of intra-cardiac shunt. CT head and neck angiography was negative for large vessel occlusions. Telemetry did not reveal any arrhythmias. Having ruled out other causes, isolated ASA was considered the likely etiology of the embolic stroke. Aspirin 81mg daily was started for secondary prevention.

Conclusion: All patients aged <60 years presenting with cryptogenic stroke should be suspected for atrial septal abnormality (PFO, ASD, ASA). In patients with isolated ASA, like our patient, it has been hypothesized that fibrin-platelet particles adhere to the left side of atrial aneurysm and get dislodged by oscillations of aneurysm causing systemic embolism. Incidental finding of atrial septal aneurysm warrants no treatment. When presenting with cryptogenic stroke, antiplatelet therapy is recommended.

WMC-21-015:

Case Report: A Clinical Case of Neonatal Alloimmune Neutropenia

Amit Aggarwal, OMS-III, Dr. Keelie Bruce, DO, FAAP, Dr. Timothy McCavit, MD, MSCS Texas College of Osteopathic Medicine, Fort Worth, TX 76107.

Background: Congenital neutropenia is a common problem in neonates and has myriad etiologies. Neonatal alloimmune neutropenia (NAIN) is among the most common causes of congenital neutropenia with an incidence of 2 per 1000 live births and has an excellent prognosis. NAIN is defined by maternally produced IgG antibodies directed against paternal and fetal neutrophil antigens, most commonly HNA-1a, HNA-1b, and HNA-2a.

Case Description: A 3-week-old female presented with omphalitis and was found to have an absolute neutrophil count (ANC) of 0. Once admitted and started on IV antibiotics, serial CBC monitoring revealed persistence of neutropenia with ANC counts <300. On hospital day 3, she was started empirically on subcutaneous filgrastim 5 mcg/kg. Due to a modest response in her ANC, the filgrastim dose was subsequently increased to a max of 30mcg/kg before discharge. Evaluations for etiologies of neutropenia included antineutrophil antibody testing, genetic testing for severe congenital neutropenia (SCN), and a bone marrow exam. SCN was the initial, provisional diagnosis. However, the bone marrow aspiration revealed marked granulocytic hyperplasia with large clusters of promyelocytes, myelocytes, and metamyelocytes and a maturation arrest at the myelocyte – metamyelocyte stage. Antibody neutrophil antibody testing was positive for the HNA-1b antibody, whereas the genetic screen for SCN did not reveal pathogenic mutations. Therefore, she was diagnosed with NAIN and was subsequently weaned off GCSF with a normal ANC.

Conclusion: This case illustrates an unusual presentation of NAIN and demonstrates the clinical heterogeneity of this disease state.

WMC-21-016:

Rate and Predictors of 30-day Readmission Among Patients with Major Depressive Disorder: a Nationally Representative Study

Zeeshan Mansuri^{1*}, MD, MPH; Chintan Trivedi^{2*}, MD MPH; Abhishek Reddy³, MD;

¹Department of Psychiatry, Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts, USA. ²St. David Medical Center, Austin, Texas, USA.

³Department of Psychiatry, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA

*Dr. Mansuri and Dr. Trivedi share equal credits for first author

Introduction: Major depressive disorder (MDD) related hospitalizations cause a substantial burden on the patient as well as the healthcare system. There is a paucity of studies readmission information among patients with MDD. We sought to evaluate the rate and predictors of 30 days readmission among MDD patients in adults (age 18-64).

Methods: Patients with the index inpatient admission for MDD were obtained from the National readmission dataset (NRD) Jan-Nov 2016. Primary outcome was the rate and predictors of 30-day readmission (RA-30). The t-test, Chi-square test, and logistic regression analysis were performed.

Results: Weighted Data of 250135 adult patients (mean age: 38 years, female: 54%) were included. Rate of 30 days readmission was 8.7% among adults (mean time to RA-30: 12.7 days). MDD was the main cause of RA-30 (50% adults), followed by other mental illness (20% adolescents, 30% adults).

In adult patients with RA-30, there was a high prevalence of personality disorders (14% vs. 11%, $p < 0.001$), psychotic disorders (6% vs. 4%, $p < 0.001$) and substance use disorders (59% vs. 54.0%, $p < 0.001$) compared to those with no readmission. There were more readmissions among male (54% vs. 45%). Slightly more patients had anxiety disorders in RA-30 group (51% vs. 50%, $p: 0.01$).

Conclusion: There is a high rate of readmission among the MDD population mainly because of the higher prevalence of comorbid psychiatric disorders. Addressing these factors may potentially help reduce the readmission rate in this vulnerable population and the associated financial burden on the hospital.

WMC-21-017:

Sensitivity and Specificity of Laboratory Biomarkers to Evaluate the Severity of COVID-19 Hospitalizations

Jigisha Rakholiya, Komal Lakhani, Payu Raval, Chika Nwodika, Chail Shah, Mehwish Martin, Harmandeep Singh, Nirmaljit Kaur, Salma Shah, Tooohukwu Okafor, Angelina Yogarajah, Urvis Patel, Mayo Clinic, Rochester, Rochester, MN 55905

Introduction: The outbreak of COVID-19 is escalating in the world. So, there is a need to recognize the laboratory predictors that could possibly assess the severity of the disease in the hospitalized patients.

Aim: To calculate sensitivity and specificity of biomarkers like D-dimer, CRP, TnI, IL-6, LDH, CK, creatinine, procal-

citonin, AST, ALT, thrombocytopenia, lymphopenia, and leukopenia.

Methods: By using Meta-analyses of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols, we searched PubMed to identify english full-text-observational studies that had data on laboratory findings and severity findings like mortality, ICU admissions, SpO₂<90%, ARDS, and invasive mechanical ventilation in COVID-19 hospitalizations between January 2020 to June 2020. Open MetaAnalyst software was used to calculate sensitivity and specificity (from individual study and overall) of biomarkers to evaluate severity. We used random-effects models to calculate odds ratio (OR) and 95%CI and to obtain forest plots and areas under ROCs.

Results: We included 31 studies with 28,106 confirmed cases of COVID-19. Our results showed that sensitivity of D-dimer was 0.63 [(95%CI:0.51-0.73);p<0.001], CRP was 0.78 [(0.67-0.86);p<0.001], Tnl was 0.35 [(0.17-0.58);p<0.001], IL-6 was 0.65 [(0.29-0.89);p<0.001], LDH was 0.70 [(0.62-0.78);p<0.001], procalcitonin was 0.37 [(0.26-0.49);p<0.001], AST was 0.51 [(0.38-0.64);p<0.001], ALT was 0.33 [(0.28-0.40);p<0.001], thrombocytopenia was 0.25 [(0.16-0.37);p<0.001], lymphopenia was 0.73 [(0.65-0.80);p<0.001], and leukopenia was 0.13 [(0.08-0.19);p<0.001] to identify severity of COVID-19 hospitalizations. The specificity of D-dimer was 0.63 [(95%CI: 0.53-0.71);p<0.001], CRP was 0.44 [(0.32-0.56);p<0.001], Tnl was 0.90 [(0.78-0.96);p<0.001], IL-6 was 0.51 [(0.20-0.80);p<0.001], LDH was 0.62 [(0.54-0.68);p<0.001], CK was 0.89 [(0.85-0.92);p=0.053], creatinine was 0.94 [(0.88-0.97);p<0.001], procalcitonin was 0.89 [(0.83-0.93); p<0.001], AST was 0.77 [(0.68-0.85);p<0.001], ALT was 0.80 [(0.74-0.85); p<0.001], thrombocytopenia was 0.85 (0.76-0.91); p<0.001], lymphopenia was 0.51 [(0.38-0.64);p<0.001], and leukopenia [0.72 (0.62-0.80);p<0.001] to identify severity of COVID-19 hospitalizations.

Conclusion: These results will provide a useful tool for clinicians in predicting and managing COVID-19 with proper utilization of available resources.

WMC-21-018:

Anxiety Disorder Among Undergraduate Medical Students of a Rural Tertiary Care Hospital of Gujarat, India Due to COVID-19 Pandemic Lockdown

Hanee D. Patel MBBS¹, Grishma D. Chauhan MBBS, MD², Dhairya Jain³, Hardil Majmudar⁴

¹ Smt. B. K. Shah Institute & Research Centre.

² Community Medicine, Associate Professor Community Medicine – Smt. B. K. Shah Institute & Research Centre.

³ 2nd year medical student, Govt. Medical College – Surat
⁴ Internship Student, Pramukhswami Medical College and Shri Krishna Hospital.

Background: Mental wellbeing is of utmost importance in the 21st century but the advent of corona virus pandemic and simultaneous lockdown has brought uncertainty, fear among other issues disturbing the normal equilibrium and leading to disharmony in mental wellbeing of university going students.

Aim: Find out prevalence and risk factors of anxiety disorder amongst undergraduate medical students of sbks medical college and research centre due to lockdown.

Methods: It was a cross sectional study. Participants were sent preformed questionnaire that included GAD-7 scale along with risk factors and socio-demographic questions via college social media groups. Students were selected by purposive sampling method.

Results: Out of the 301 responses analysed, results indicated 11.63% were screened to be experiencing severe anxiety, 19.27% moderate anxiety, 29.57% mild anxiety. Disturbance in academic study schedule ($r = 0.378$, $P < .001$), inability of the participants to go outside as a routine ($r = 0.234$, $P < .001$), inability to perform extracurricular activities ($r = 0.160$, $P = .006$) and the lack of offline/On campus experience were significant factors leading to increased anxiety for the students ($r=0.322$, $P<0.001$).

Conclusions: The COVID-19 lockdown had created a significant anxiety among the medical students. Lockdown related impact on the mental wellbeing of students is on rise and interventions have to be devised to prevent further mental deterioration and treat anxiety via counselling or pharmaceutical measures.

WMC-21-019:

Case Report: Delayed Recovery of a Prolonged Total IntraVenous Anesthesia Procedure with Risks of Malignant Hyperthermia

Amit Aggarwal, OMS-III, Annum Faisal, OMS-III, Dr. Mahammad Hussain, MD; Texas College of Osteopathic Medicine, Fort Worth, TX 76107

Background: Spinal Cord Ependymoma (SCE) is an intramedullary tumor that requires surgical intervention. Total Intravenous Anesthesia (TIVA) is indicated for such neurosurgery cases. The pharmacodynamics and pharmacokinetics of each drug used must be factored to safely extubate and maintain the airway postoperatively.

Case Description: A 57-year-old male with a history of pulmonary hypertension presented to the hospital with complaints of gait difficulty and sensory deficits secondary to SCE. The patient was scheduled for surgery, and the

decision was made to do TIVA due to a family history of Malignant Hyperthermia. Three continuous IV drips were placed: propofol, titrated between 125-300 mcg/kg/min, ketamine at 5 mcg/kg/min, and sufentanil at 0.3 mcg/kg/hr. The patient required a phenylephrine infusion at 35 mcg/min to maintain hemodynamics, which had to be titrated up to 75mcg near the 11-hour point due to severe hypotension. Following extubation, the patient was placed on an oral airway with a simple O2 mask in place. He was noted to have snoring respirations with oxygen desaturating to the low 80's. A jaw thrust was done, and he was placed on a non-rebreather mask. Due to a fixed obtunded state, a hasty decision to re-intubate was made without proper reevaluation and communication between providers. The patient was then re-extubated 1.5 hours later with minimal post-op complications.

Conclusion: This case illustrates the challenges of prolonged TIVA in the assessment of safely extubating patients while maintaining the airway in the postoperative period.

WMC-21-020:

Von Recklinghausen Disease – Seizures and Gliomas – A Case Report

Jonathan Quinonez DO¹, Sylvia Paesani MD², Samir Ruxmohan DO³, Wilson Cueva MD⁴

¹ CannaMD, Tampa, FL

² Larkin Community Hospital, Miami, FL

³ Larkin Community Hospital, Miami, FL

⁴ Larkin Community Hospital, Miami, FL

Background: Von Recklinghausen disease (Neurofibromatosis type 1, NF1) refers to an autosomal dominant genetic disorder that is characterized by the development of multiple benign (non-cancerous) tumors that impact the nervous system and skin (neurofibromas). This disorder has a prevalence of one in 3,000 births and a high frequency of mutation leading to variable presentations ranging from benign lesions to nonfunctional impairment with complications. Such complications vary based on age and can include psychiatric disorders (anxiety, dysthymia, depression), chronic low back pain with scoliosis, and even seizures. NF1 has a higher seizure prevalence compared to the general population; however, the rationale behind this is difficult to elucidate due to when and how seizures are diagnosed as well as if provoking factors are present.

Case Description: We present a case report of a 20-year-old male with a documented history of NF1, since the age of three, who presented to a local hospital for evaluation of an unwitnessed seizure with loss of consciousness/bladder control. He underwent an MRI without contrast which demonstrated hyperintensities bilaterally over the

mesial temporal lobe along with a FLAIR hyperintensity lesion near the splenium of the corpus callosum. He later became combative and experienced another seizure event requiring intubation. A repeat MRI with contrast demonstrated a faint enhancement of the splenial lesion. He later underwent EEG monitoring which was unremarkable.

Conclusion: We present a case with a tumor of the splenium of the corpus callosum and NF1. The imaging characteristics provide a possible rationale for a higher seizure frequency in NF1 patients compared to the general population.

WMC-21-021:

Rosai-Dorfman: Rare Disease with Atypical Renal and Pulmonary System Involvement

Rahul Bhalla ¹, Aakash Desai ², Philip Konits (MD) ³

¹Trinity School of Medicine (trinityschoolofmedicine.org)

Rahul.bhalla.20@trinitysom.net

²GMERS Medical College and Hospital, Sola, Ahmedabad, India (www.gmersmchsola.com/home)

Aakashkdesai@gmail.com

³General Oncology/Hematologic Oncology, Bon Secours Hospital- Baltimore, University of Maryland

Medical Center Midtown Campus, Ascension St. Agnes Hospital-Baltimore, Sinai Hospital of Baltimore, Northwest Hospital, Carroll Hospital Center

pkonits@yahoo.com

Also known as sinus histiocytosis with massive lymphadenopathy, this is a rare disorder of unknown cause. It typically presents with an accumulation of histiocytes in the lymph nodes or other locations in the body. This histiocyte build up can cause lymphadenopathy in lymph nodes or extranodal disease if outside in another part of the body. The most common sites of extranodal disease in Rosai-Dorfman patients are skin, nasal cavity, paranasal sinuses, soft tissue, eyelid/orbit, bone, salivary glands, and central nervous system. Symptoms and physical features of this disease vary greatly from patient to patient depending upon the extent to which this disorder affects parts of the body. This disorder mainly affects children, adolescents, or younger adults specifically males. Langerhans cell histiocytosis is one of the most common differential diagnosis related to Rosai-Dorfman disease.

Our patient, a 28-year old African American male, presents with a very unique set of complications with multiple organ system involvement manifesting from Rosai-Dorfman disease (RDD). This patient exhibits renal and pulmonary involvement which is a very rare combination that has rarely been reported. RDD is a disease of nonmalignant histiocytes that infiltrate lymph nodes or extranodal

tissues. RDD cells exhibit emperipolesis, the nondestructive phagocytosis of lymphocytes or erythrocytes, which is the hallmark of the disease and required for diagnosis. The etiology of RDD is unknown and is considered an idiopathic histiocytosis. In the setting of RDD, grossly involved lymph nodes are enlarged and matted with thickened capsules. On microscopic examination with H and E stain, the normal lymph node architecture is altered by massive sinusoidal dilation that contains histiocytes, lymphocytes, and plasma cells. The intact lymphocytes, plasma cells, and erythrocytes inside the histiocytes are contained in the intracellular vacuoles, thus allowing an escape from degradation by the cytolytic enzymes during their transit through the histiocyte cytoplasm. In addition to the histiocytic proliferation in the dilated sinusoids, reactive lymphoid follicles may be present in the cortex of the lymph node.

Keywords: Rosai-Dorfman, multiple organs, extranodal disease, CD68+, renal mass, upper lobe cavitory lesion, emperipolesis

WMC-21-022:

Giant Right Coronary Artery Aneurysm Mimicking A Right Intra-Atrial Mass: A Case Report

Minakshi Singh MD, Rajiv Aggarwal MD, Vineeth Nagubandi MBBS.

Lansdowne Travel & Family Medicine, 1860 Town Centre Dr., Suite 340, Reston VA 20190

Background: Coronary artery aneurysms (CAAs) are focal dilation of a coronary segment (≥ 1.5 times the adjacent regular segment). Etiological factors include atherosclerosis, Takayasu arteritis, congenital disorders, Kawasaki disease (KD), and percutaneous coronary intervention. Potential complications are thrombosis, rupture, and embolism. "Giant" CAA is generally referring to a dilatation that exceeds the reference vessel diameter by four times, and the reported incidence is 0.02%.

Case Presentation: We present an interesting case of 66 years old female encountered to establish primary care with presenting complaints of right lower leg cellulitis. Echocardiography was ordered considering the previous history of MRSA positive cellulitis and decreased exercise tolerance. A preliminary diagnosis of Right atrium cystic tumor was made. Further radiological evaluations confirmed a giant right coronary artery aneurysm—the potential near-miss timely managed by exclusion surgery.

Conclusion: Giant coronary artery aneurysm mimicking an intra-cardiac mass are extremely rare and poorly understood. Coronary artery aneurysm is mostly detected incidentally on an angiogram or at autopsy. However, an aneurysm could be suspected by a competent family

physician in patients with a varied cardiac presentation. Comprehensive preoperative evaluation is highly recommended because surgical strategies for tumors and aneurysms are entirely different.

WMC-21-023:

Risk Factor Assessment for Type-2 Diabetes Mellitus in the Patients Attending Diabetic OPD in SVP Institute of Medical Science and Research

Nisarg Dave, M.B.B.S Dept. of Medicine, Smt. NHLMMC, SVP Institute of Medical Science and Research, Ahmedabad, India.

Background: Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia resulting from a diversity of aetiologies, environmental and genetics acting jointly. It has been an "Iceberg" disease.

Aim/Hypothesis: To study the socio-demographic correlates of diabetic people attending SVP hospital diabetic OPD. To identify the relevant risk factors in already diagnosed cases of type-2 diabetes mellitus and to provide health education.

Methods: This study was conducted on 50 diabetic patients and 50 non-diabetic patients attending diabetic and general medicine OPD respectively, from October 2019 to December 2019. After taking permission from dean, we started collecting information on pre-tested and pre-designed proforma which contains 2 parts. 1) Sociodemographic information of respondent 2) Information regarding assessment of risk factors. Data thus collected, was compiled and analyzed using suitable statistical tests.

Results: Here, a greater number of diabetic patients are in age group 51-60 yrs. (32%), followed by 30% in 41-50yrs. 53% of males and 46% of females were found diabetic. Amongst them, 89% of males and 71% of females were obese. It is associated with past h/o surgery (58%) and urbanization (82%). Diabetic patients are less commonly associated with alcohol (10%), smoking (20%), and perceived stress (18%). 64% belong to class I socioeconomic status, 48% have family h/o diabetes and 90% of patients have sedentary activity. The Standard deviation in socioeconomic status in diabetic is 12.78 and in non-diabetic is 8.83. Odds ratio for obesity in diabetic males is 34.6 and chi-square is 26.61. In diabetic females it is 6.43 and chi-square is 8.77. Odds ratio in sedentary activity is 3.86 and chi-square is 6.25. Odds ratio in urbanization is 1.60.

Conclusion: From this study, we can infer that major risk factors for diabetes mellitus are obesity, sedentary activity, high socioeconomic status, urbanization, past h/o surgery, and family h/o diabetes.

WMC-21-024:

Primary vesical Actinomycosis with Changes of Cystitis Cystica Presenting as Bladder Mass

Dr. Charmy Parikh(Medical Intern), Dr. Henil Upadhyay (Medical intern), Dr. Nagendra Mishra(Consulting Urologist); Pramukhswami Medical College

Abstract: Primary vesical actinomycosis is an extremely rare infection with only a few cases reported in literature. It is commonly misdiagnosed as a bladder mass and definitive diagnosis is only possible after histopathological examination of the infected tissue. We present a case primary vesical actinomycosis which was diagnosed with bladder mass based on clinical and radiological reports. However, histopathological reports confirmed Actinomycosis with changes of cystitis cystica. The patient was successfully managed with amoxicillin and potassium clavulanate. We need to consider Actinomycosis as a differential diagnosis in cases presenting as bladder mass as both diseases have different treatment modalities and prognosis.

WMC-21-025:

A Case of Systemic Lupus Erythematosus with Seizure Disorder

Kunwardeep Arora, MBBS ¹, Anurag Arora DM ²
Aastha Neuroresearch and Rehabilitation Center

Background: Systemic lupus erythematosus (SLE) is an autoimmune systemic disease characterized by a broad spectrum of clinical manifestations that may also affect the central nervous system. A seizure is one of the most common Neuropsychiatric SLE manifestations of disorder yet potentially fatal disease.

Aim: The diagnosis of autoimmune epilepsy is often challenging and can be misdiagnosed as epileptic disorders or viral encephalitis. Autoimmune epilepsy has a strong association with systemic lupus erythematosus (SLE).

Case Description: A 25-year female patient presented with recurrent seizures for the last 3 days not responding to the standard anti-epileptic medications. After careful evaluation of the patient, she was found to have mouth ulcers, low WBCs, and low platelet counts. We ordered various investigations to rule out the causes of seizures. The tests included EEG, MRI, lumbar puncture showed no possible findings to explain the cause of status epilepticus. Additionally, we found out that ANA and anti-dsDNA were positive fulfilling the criteria for the diagnosis of SLE. Subsequently, we confirmed that the seizures were one of the common symptoms among patients with NPSLE. Following which the patient was hospitalized for 10 days

and was treated with methylprednisolone to which she responded and is being followed up and she showed no signs of recurring epileptic seizures and flares or symptoms of SLE.

Conclusion: The case report highlights the importance of studying autoimmune epilepsy associated with autoimmune diseases and considering it into the range of differential diagnoses. Autoimmune epilepsy should call the attention of the clinicians, especially when the patient presented with SLE. Moreover, this study shows that speedy diagnosis may be proved helpful in decreasing mortality and morbidity thereby letting effective treatment.

WMC-21-026:

Atypical Presentation of Postpartum Psychosis: A Mixture of Retarded and Excited Features of Catatonia

Batool Sheikh, MD ¹, Divya Periasamy MD ²
Brookdale Hospital Medical Center, New York

Background: Catatonia is a syndrome of psychomotor symptoms. There are two subtypes of catatonia; retarded and excited. Cases have been reported where patients presented with postpartum psychosis mostly with retarded catatonia. Our case report showed postpartum psychosis with symptoms of retarded and excited catatonia concurrently.

Aim: The aim is to bring the awareness of atypical symptoms of catatonia in patients with postpartum psychosis in order to reduce morbidity and mortality.

Case Description: An 18-year old female with history of with ADHD, postpartum day 30, presented with disorganized behavior sitting on a toilet seat for hours not responding to verbal stimuli. Patient was admitted for proctitis due to inserting unrelated objects in her anus. On initial psychiatric evaluation the patient exhibited disorganized and stereotyped behavior, attempting to insert plastic utensil in rectum. On follow up, she presented with retarded symptoms of catatonia which included mutism, immobility, staring and withdrawal. Bush-Francis Catatonia Rating Scale (BFCRS) score 18. Patient was started on Lorazepam. Within hours patient was exhibiting excited symptoms of catatonia including combative, impulsive and stereotypy behavior. BFCRS score increased to 24. Patient was transferred to inpatient psychiatry for management of acute psychosis. Patient was treated with Lorazepam and Haloperidol for catatonia and psychosis respectively. She improved significantly overtime and was discharged on baseline.

Conclusion: Postpartum psychosis can present in different ways. Our patient presented with an atypical presentation of postpartum psychosis with both subtypes of catatonia.

Her symptoms were fluctuating rapidly and diagnosis was challenging due patient's atypical presentation. However, she received proper treatment and reached the baseline. Postpartum psychiatric illnesses are serious conditions and can lead to suicide or infanticide. The evaluation should be comprehensive and differential diagnosis should be broad to prevent any misdiagnosis.

WMC-21-027:

Post-naloxone Neurologic Recovery in a Patient with a Bilateral Thalamic Stroke: a Case Report

Hyder Tamton DO, Samir Ruxmohan DO, Ricardo Martinez MD, Amin Abolfazli MSc, Muneer Bhaiyat BSc, Wilson Cueva MD

Larkin Community Hospital, Department of Neurology, 7031 SW 62nd Ave, South Miami, FL 33143

Aim: To present a case of bilateral thalamic ischemic stroke with pinpoint pupils that demonstrated an immediate post-naloxone administration wakefulness and neurologic recovery.

Background: This is an 81-year old male with a history of hypertension admitted with altered mentation and acute hypersomnolence. Labs and vitals were unremarkable. The patient received one dose of naloxone by EMS to no response. Non-contrast CT head and urine toxicology were unremarkable. The patient was stuporous, but could protect his airway. Neurological examination was non-focal; however, the patient was found to have noticeable bilateral pinpoint pupils. The patient was then given two more doses of naloxone. The patient then became awake, alert, verbal and oriented. The pupils immediately normalized. He maintained this level of appropriate consciousness throughout the day and remained non-focal. The next morning, however, the patient was found to have an impaired downward gaze bilaterally. MRI of the brain demonstrated bilateral thalamic restricted diffusion, consistent with an artery of Percheron infarct.

Conclusion: Based upon our review of current literature, temporary 24-hour neurologic reversal by naloxone administration in a patient with an ischemic stroke is a rare occurrence. Our case is unique in that this patient with pinpoint pupils and bilateral thalamic stroke showed immediate recovery with naloxone administration. The lack of neurologic response in some case reports is possibly due to insufficient dosage of naloxone. Additionally, there are different types of Mu opiate receptors with different sensitivity to naloxone. Further research regarding naloxone's disinhibitory actions can offer insight to other pathologies such as infection or autoimmune diseases that could potentially also be temporarily reversed by naloxone administration.

WMC-21-028:

A Rare Case of Malignant Peritoneal Mesothelioma Presenting with Non-specific Symptoms at Later Stage of Malignancy

Avantika Israni MD¹, Sameer Dawoodi MD²

¹ St. Mary Medical Center, PA

² Yale Bridgeport Hospital, CT.

Introduction: Malignant mesothelioma is a highly lethal malignancy with incidence of 1.94 (men) and 0.41(women) per 100,000 and approximately 3300 cases of mesothelioma diagnosed in the United States every year, only 10 to 15 percent are peritoneal. We are presenting a 71-year-old male presented with non-specific symptoms that ended up diagnosed with malignant peritoneal mesothelioma.

Case Report: A 71-year-old male with multiple vascular risk factors hypertension, hyperlipidemia, type 2 diabetes mellitus, ischemic stroke and a history of iron deficiency anemia presented to the ER with non-productive cough, dyspnea for 2 days. He reported some blood per rectum, nausea, and vomiting. He also complained of abdominal distension and bloating for 3-4 days. A review of system was positive for generalized weakness, left sided weakness, poor appetite, and abdominal bloating. His past medical history is significant for diverticulitis and benign prostatic hypertrophy and heavy tobacco use quit 3 years ago. His family history is significant for head and neck cancer. Physical exams and vitals are within normal limits. His labs were significant for Hemoglobin of 9.7 g/dl, MCV of 79.6 fL, Iron 14 mcg/dL, TIBC 164 mcg/dL, Ferritin 2790ng/mL, CRP 292.60 mg/L and D-Dimer 550 ng/mL. Microbiology for COVID 19, Legionella, Stool PCR were negative. Chest X-ray demonstrated patchy infiltrates throughout the lungs most prominently in the right base concerning for an underlying infectious/inflammatory process. Fullness of central pulmonary vasculature. CT abdomen demonstrated 3.2 x 2.2 cm mediastinal-cardiophrenic lymph node, large ascites with concern for soft tissue masses throughout the omentum highly suspicious for peritoneal carcinomatosis with questionable gastric wall thickening. There was also moderate right sided pleural effusion which was drained concerning for malignant effusion, however, cytology was negative for the same.

He subsequently underwent upper GI endoscopy for suspicion of gastric cancer. He was found to have a gastric tumor in the fundus and on greater curvature of the gastric body which was biopsied. The biopsy was negative for neoplasia. He underwent paracentesis and cytology showed reactive mesothelial cells, no malignant cells. Eventually, he underwent a diagnostic laparoscopy and omental and peritoneal biopsy, excision of umbilical nodule.

Omental and peritoneal biopsy was diagnostic for malignant mesothelioma. Pathology report suggested the malignant cells are positive for calretinin, CK5/6, CK7 and CAM5.2. Focal p53 staining is present. Non-specific staining is seen with GATA-3. They are negative for BER-EP4, PAX-8, CK20, CDX2 and TTF-1. The histomorphology and immunohistochemical findings are consistent with malignant mesothelioma. Metastatic Mesothelioma/NCCN guidelines for stage 3 was diagnosed and the palliative care was consulted and the patient and his family decided to transition to hospice care.

Conclusion: Malignant peritoneal mesothelioma with pleural involvement is a very rare disease of peritoneal surfaces which is diagnosed less frequently. Systemic chemotherapy and other cytoreductive surgery could be a possible choice if it may be diagnosed at an early stage.

WMC-21-029:

Late Metastatic Recurrence of Renal Cell Carcinoma in Right Ventricle

Arashdeep Rupal^{1,2}, Chinmay Jani^{1,2}, Harpreet Singh³, Aymen Elfiky^{1,2,4}

¹Department of Medicine, Mount Auburn Hospital, Cambridge, MA; ²Harvard Medical School, Boston, MA

³Division of Pulmonary and Critical Care, Medical College of Wisconsin, Milwaukee, WI; ⁴Division of Hematology-Oncology, Mount Auburn Hospital, Cambridge, MA

Introduction: Cardiac metastasis from renal cell carcinoma (RCC) without involvement of inferior vena cava is extremely rare. Late recurrence in the heart, defined as recurrence more than 10 years after nephrectomy for primary RCC, is even more infrequent. We present a case of a patient who had late metastasis of RCC to the right ventricle 12 years after nephrectomy for primary disease.

Case Presentation: A 78-year-old man with a history of clear cell RCC (AJCC pathological stage: pT3, pNX, pMX) status post nephrectomy in 2008 presented with progressive dyspnea and unintentional 13lb weight loss over the past 3 months. A chest x-ray revealed tracheal deviation, and a subsequent CT scan of the neck and chest revealed a large mass in the upper mediastinum and a filling defect within the apex of the right ventricle (RV). TTE revealed an RV apical mass measuring 3.0 x 2.5 cm without RV outflow tract obstruction, which was confirmed with cardiac MRI. Cardiac catheterization was unrevealing. PET scan revealed minimal metabolic activity involving the mediastinal mass and right ventricular mass without abnormal uptake elsewhere. The patient underwent RV tumor resection with pericardial patch placement. Post-operative pathology confirmed metastatic disease from a clear cell RCC.

Discussion: The accepted treatment for late isolated metastatic recurrence of RCC is wide local excision with histological free margins. Immunotherapy and/or molecularly targeted therapy may be considered as adjuvant treatment or alternative to surgery for unresectable tumors. Solitary metastases, a long disease-free interval, and complete excision of the tumor confer a good prognosis.

Conclusion: Late cardiac metastasis presents a unique disease course in RCC. Presentation is usually nonspecific and requires a high index of suspicion for diagnosis. Long-term surveillance based on risk stratification may aid in prompt diagnosis and timely intervention in such cases.

WMC-21-030:

Pitolisant for the Treatment of Excessive Daytime Sleepiness in Narcolepsy: A Meta-Analysis of Randomized Controlled Trials

Zeeshan Mansuri^{1*}, MD, MPH; Abhishek Reddy^{2*}, MD; Ramu Vadukapuram³, MD; Chintan Trivedi⁴, MD MPH

¹Department of Psychiatry, Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts, USA. ²Department of Psychiatry, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA ³Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴St. David Medical Center, Austin, Texas, USA.

*Dr. Mansuri and Dr. Reddy share equal credits for first author

Introduction: Pitolisant is a histamine receptor (H3R) antagonist/inverse agonist approved by the Food and Drug Administration for treatment of excessive daytime sleepiness (EDS) in narcolepsy. We sought to perform a meta-analysis assessing safety and efficacy of Pitolisant in EDS.

Methods: Relevant randomized controlled trials of Pitolisant were identified from Pubmed and Google Scholar database from inception through July 2020. Data were collected from the studies on the Epworth Sleepiness Scale (ESS) score change and patient global opinion (PGO) on efficacy and adverse events. Data were compared using inverse variance method and Mantel-Haenszel method. Odds ratio (OR) and the mean difference were used to present summary effect for continuous and categorical data. The fixed-effect model was used for all the analyses except for side effects, where the random effect model was used because of heterogeneity. Heterogeneity was assessed using I² statistics.

Results: Three studies (286 Pitolisant and 148 Placebo) met inclusion criteria. Two studies were on patients with narcolepsy (age: 18-66, male: 52%) and one study on patients with obstructive sleep apnea (age: 25-76, male: 75%). After 7 to 12 weeks, Pitolisant was associated with improvement in ESS score with mean reduction of -3.06 (-3.97, -2.15, $p < 0.001$). More patients were treatment responders measured by $ESS \leq 10$ (OR: 2.90, $p < 0.001$) in the Pitolisant group. Also, more patients on Pitolisant had improved opinion on efficacy (OR: 3.89, $p < 0.001$). Headache (OR: 1.05, 0.88) and nausea (OR: 2.00, $p: 0.28$) were similar between the groups. There was no difference in side effects between the groups (OR:1.74, $p:0.16$). There were no serious adverse events in any of the groups.

Conclusions: Pitolisant use is associated with improvement in excessive daytime sleepiness compared to placebo, is well-tolerated and not associated with serious side effects. Additional studies are needed to confirm these results in larger populations.

WMC-21-031:

Understanding Parinaud's Syndrome: Pathophysiology of the Signs and Symptoms

Juan Fernando Ortiz, Samir Ruxmohan, Ammar Alli, Victor A. Orellana, Álvaro Morillo Cox Larkin Community Hospital, Miami, FL, South, Miami, FL 33143

Purpose: Understand the pathophysiology of the signs and symptoms of Parinaud's syndrome

Methods: We did an advanced search strategy and a MeSH subheading search strategy using the terms. We included only studies conducted in humans in the last 25 years, written in English language.

Results: After applying the inclusion/exclusion criteria we gathered 25 papers for the discussion of the paper.

Conclusion: Parinaud's syndrome's main symptoms are diplopia, blurry vision, visual field defects, ptosis, squint, and ataxia. Diplopia is caused mainly due to involvement of the IV nerve. Blurry vision is related to accommodation problems, while the visual field defects are thought to be a consequence of chronic papilledema that causes optic neuropathy. The ptosis in Parinaud is caused by damage of the oculomotor nerve. We did not find a good explanation for squint. Finally, ataxia is caused by compression of the superior cerebellar peduncle. Parinaud's syndrome's main signs are upward gaze paralysis, upper eyelid retraction, convergence/retraction nystagmus (CRN), and pseudo-Argyl Robertson pupils. Two nuclei are involved in the upward gaze palsy, riMLF and Cajal's. When downgaze is compromised, there is an involvement of the posterior commissure or pretectal area. Collier's sign occurs when there is damaged of the posterior commissure. The

posterior commissure controls the saccade's speed have and inhibited the eyelid upgaze. CRN is a vergence anomaly, not a saccadic anomaly. CRN arises from a dysfunction of rostral interstitial nuclei of the riMLF and the posterior commissure. In CRN, there is a continuous discharge of the medial rectus muscle because of the supranuclear fibers' lack of inhibition. External compression of the posterior commissure causes the pseudo Argyl Robertson pupils. Pseudo-Argyl Robertson pupils conserved some response to light because there is an additional pupillary light response pathway that involves attention to a conscious bright dark stimulus.

WMC-21-032:

Patent Foramen Ovale and Ascending Aortic Dilation causing Platypnea-Orthodeoxia Syndrome

Harpreet Singh*¹, Chinmay Jani *^{2,3}, Arashdeep Rupal^{2,3}, Alexander Walker^{2,3}, Omar Al Omari^{2,3}

¹Division of Pulmonary and Critical Care, Medical College of Wisconsin, Milwaukee, WI, USA. ²Department of Medicine, Mount Auburn Hospital/Beth Israel Lahey Health, Cambridge, MA, USA. ³ Harvard Medical School, Boston, MA, USA

Introduction: Platypnea-orthodeoxia syndrome (POS) is characterized by dyspnea (platypnea) and hypoxemia (orthodeoxia) in upright position that resolves when recumbent. Several intracardiac and pulmonary mechanism are described causing right to left shunt in upright position. We report a case of patent foramen ovale (PFO) and a dilated ascending aorta presenting as POS.

Case Narration: A 68-year-old male with past medical history of COPD, sleep apnea, ascending aortic dilation (3.9 cm), myelofibrosis, and graft versus host disease was found hypoxemic (oxygen saturation 82%) on routine visit prompting hospitalization. Hypoxemia responded to 40% Fio₂ initially but subsequently progressed to refractory hypoxemia (oxygen saturation 83%-85%) on 100% Fio₂. Chest CT scan showed evidence of multiple segmental pulmonary emboli. Hypoxemia out of proportion to pulmonary embolism clot burden and examination findings consistent with orthodeoxia prompted further investigations. Nuclear medicine scan showed right to left shunt (5.9%). TEE revealed PFO. Right heart catheterization consistent with right to left shunt (QP/QS 0.74) and normal right heart pressures. PFO was closed with transcatheter closure device leading to immediate resolution.

Discussion: POS requires an anatomical factor such as PFO, and a functional factor such as aortic aneurysm, pericardial effusion, emphysema which promotes abnormal shunting when the patient rises from recumbent to an upright position. In our patient, redirection of flow from right-to-

left was caused by an anatomical distortion of right atrium or atrial septum secondary to aortic dilatation. TTE, TEE, and right heart catheterization are the diagnostic modalities. Left heart cardiac catheterization remains gold standard to show mismatch in oxygen saturation between pulmonary vein and aorta.

Conclusion: POS should be suspected when patient's hypoxemia in upright position resolved when recumbent. Identification and correction of shunting often lead to complete resolution. Our patient's PFO was successfully closed by percutaneous transcatheter closure device leading to complete resolution of hypoxemia.

WMC-21-033:

Natural History of Wolf-Hirschhorn Syndrome: Experience with A Patient Encounter

Angel Sunny, MBBS^{1,2}

¹ JSS Medical College, Mysuru, Karnataka, India

² Peekaboo Pediatrics, Houston, Texas

Background: Wolf-Hirschhorn syndrome is a rare genetic condition, with disorder features that include seizures, dysmorphic facial appearance, delayed growth, and intellectual disabilities. This extremely rare chromosomal disorder occurs in 1 in 50,000 births however the statistics can be underestimated due to the likelihood that some affected individuals are never diagnosed. The genetic mechanism of Wolf-Hirschhorn syndrome is based on the deletion of the distal portion of the short arm of chromosome 4 (4p).

Aim: Offer readers recognition pattern to identify Wolf-Hirschhorn syndrome in their practice.

Case Description: The patient from my case report was born preterm at 35 weeks' gestation via the cesarian section. He was admitted to NICU for 26 days for hypothermia, reduced oral intake, jaundice, and low birth weight. The neonatologist in the NICU noted mild dysmorphic features and advised to take a genetic study. Cardiology evaluation showed atrial septal defect and patent foramen ovale with pulmonary hypertension. At the age of two months, he had a sepsis event and was hospitalized with detailed work involving several neonatal specialists. Nephrology workup showed the presence of bilateral cortical renal cysts. Due to poor eye tracking and seizure, ophthalmology and neurology workup had been done which showed hypoplastic corpus callosum, leading to the patient being started on Keppra (Levetiracetam). At the age of three months, he showed delayed physical and neurocognitive development and a characteristic appearance, which led to a specialist consultation to diagnose the genetic disease.

Conclusion: On the basis of clinical and laboratory findings the boy was diagnosed with Wolf-Hirschhorn syndrome. The baby is now 18 months old and needed hospitalization multiple times, with the plan of care involving symptomatic treatment including multiple specialties.

WMC-21-034:

Tianeptine Abuse Among Adult Attention Deficit Hyperactivity Disorder (ADHD) - A Rare Case Report

Saral Desai MBBS¹, Richa Jaiswal MBBS, MSCR², Syeda Gul-e-Zehra Rizvi MD³, Sarah Hanif MD⁴, Suraiya Silvi MD⁵, Puneet Singla MBBS⁶, Ya-Ching Hsieh MD, MPH⁷ and Tapan Parikh MD, MPH⁸

¹Surat Municipal Institute of Medical Education & Research, India; ²Medical university of South Carolina, SC, USA; ³BronxCare Health System, NY, USA; ⁴Tulane University School of Medicine, OK, USA; ⁵Millwood Hospital, TX, USA; ⁶Government Medical College, Patiala, India; ⁷Icahn School of Medicine Mount Sinai, NY, USA ⁸Northwestern University of Feinberg School of Medicine, IL, USA

Background: Tianeptine is an atypical tricyclic antidepressant prescribed for depression and anxiety disorder. Despite being FDA unapproved in the US, it is sold online as a supplement.

Aim: We report a case of a 32-years-old male using tianeptine as a supplement outside the therapeutic dosage for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and developing tolerance and dependence overtime.

Case Presentation: A 32-year-old male presented to a clinic in Ozark, MO with the complaint of being 'hooked' on his ADHD supplement. He complained that stimulant medication that he was using since childhood for ADHD lost its efficacy after prolonged use and he started experimenting with ADHD supplements including tianeptine. He initially started with 60mg/day tianeptine purchased from online vendors and reported improved mood and motivation, but lost these effects after 4 weeks of daily usage. As a supplement, he felt safe to increase dosage to 180mg/day to achieve those initial effects and continued to escalate his dosage, reaching 900mg/day. Eventually, he found it financially difficult, and decided to stop using it. Within 5 hours of discontinuation, he experienced dysphoria, nausea, sweating, palpitations, GI upset, and tremors that resolved after ingestion of tianeptine. For the next two months, his repeated attempts to discontinue tianeptine were unsuccessful. Finally, he decided to visit Urgent Care where he was given benzodiazepines for withdrawal symptoms and eventually referred to ER for further management.

Conclusion: This case highlights the need to recognize and educate patients of potential abuse of tianeptine and its ability to produce physical dependence after prolonged use. Our case also emphasizes the need to have strict regulation over the purchase and distribution of tianeptine in the United States.

WMC-21-035:

A Medical Student Perspective on Online Lectures Conducted during COVID Pandemic- A Cross-sectional Study

Raghunandan Ramanathan¹, Dr. Balaji Arumugam²

¹Third Year MBBS, Tagore Medical College and Hospital.

²Professor and Head, Department of Community Medicine, Tagore Medical College and Hospital.

Introduction: The Global academic calendar has been thrown into a state of disarray by covid-19 outbreak. Most of the medical colleges promoted online education as a solution to this crisis. It is necessary to assess whether students are satisfied with the mass online learning in the medical colleges.

Objective: To describe and analyse the pattern, utilisation and learning experience of online classes by medical students during COVID Pandemic.

Materials and Methods: Study Design: Cross Sectional Study; Study Area: Tagore Medical College & Hospital; Study Period: October And November 2020; Study Population: Ug Medical Students From 1st To 4th Years. Sampling Technique: Convenient Sampling; Sample Size: 127; Study Tool: Structured and Validated questionnaire with a pilot study on sample of 30. Data Collection: Self-Administered Google Form; Data Analysis: The data is entered into Microsoft excel and then frequencies are calculated for each variable.

Results and Discussion: Total number of respondents were 127 with mean age of 20.4 in which 60% were females and 40% are male. Among them 75% are from urban areas. 94.5% of students attended their classes regularly and 87% attended for more than 2 months. Among them, 47% of students had classes of 7-9 hours per week. 70% of students faced difficulty in attending online lectures and majority (27%) had poor internet connection. 47% students feel difficult in raising doubts in online lectures and about 81% students have average to poor concentration while 82% had average to poor experience in online classes. 85% prefers classroom lecture than online lecture.

Conclusion; Students prefer regular classroom lectures than online classes in this study may be due to the primary challenges in E Learning such as technical difficulty and lesser space for interaction. E Learning is set to grow in high speed and research must be carried out on larger

scale to facilitate improvement in methods of teaching and learning.

Reference: John Demuyakor. (2020) Coronavirus (COVID-19) and Online Learning in Higher Institutions of Education: A Survey of the Perceptions of Ghanaian International Students in China. *Online Journal of Communication and Media Technologies* 10:3, pages e202018.

WMC-21-036:

A Curious Case of Gustatory Mystery

Ammu Susheela MD, Jogeet Sikhon MD, Komal Kaul MD
Loyola-MacNeal Hospital: 3249 S Oak Park Ave, Berwyn, IL 60402

Introduction: Geriatric care requires a broad knowledge about various chronic ailments of elderly. Here we have an interesting case of a veteran who came with a mysterious condition of lack of taste for over 2 years which was causing him a great deal of functional disability.

Case Report: A 71y-old veteran male with significant history of insomnia, somnambulism, multiple falls, hypothyroidism, hypertension, hyperlipidemia, anxiety, IBS, migraine, OA, anorexia, IHD and anorexia from ageusia and weight loss (50 lbs in 1 year). Patient was not able to taste anything for the past 2 years and he had been to several doctors for his condition. He became skin and bones due to lack of eating as he was not able to taste anything. Due to severe anorexia and malnutrition, a PEG tube was placed at Palos Hospital. He had one feeding following which he had severe diarrhea and went to the bathroom and felt lightheaded and lay on the floor of the bathroom. His wife called 911 and after reaching ED, he was given fluid bolus and was feeling better. In the hospital, a nutritionist was consulted and pump feeding was started through the G tube. He was also found to have sinus bradycardia, orthostatic hypotension and he was given fluids and his BP medications were held. He was also noted to have marked macrocytic anemia and transfused 1 unit of RBC. He also has been on a high dose of levothyroxine and TSH was found to be 0.01, Free T4 2.1. Levothyroxine was held. His B12 was found to be <91 and he mentioned that he stopped taking B12 20 Years ago when his PCP changed. He was given 1000 mcg of B12 injection IM and he mentioned that for the first time in 2 years, he was able to taste food and his appetite improved. He could be fed by mouth and no longer wanted to be fed by PEG tube. He was also found to have low liver enzymes, lymphopenia and thrombocytosis which could be attributed to malnutrition and B12 deficiency. His condition stabilized and his strength improved. He was discharged home with close PCP follow up at Palos for weekly B12 injection, TSH follow up for restarting his thyroid medication and BP monitoring for his restarting his

BP and BPH medication. He was also advised to follow up with his GI doctor regarding his PEG tube and the futility of it.

Conclusion: This case depicts an interesting manifestation of B12 deficiency. Chronic ageusia should trigger a work up for B12 investigation as it is an easily reversible cause of ageusia. This case also showed the importance of continuity of care as loss of follow up and miscommunication among providers lead to missing out on an established diagnosis and very serious procedure of PEG tube placement for a reversible cause of dysgeusia and anorexia.

Reference: Mundt B, Krakowsky G, Röder H, Werner E. [Loss of smell and taste within the scope of vitamin B12 deficiency]. *PsychiatrNeurol Med Psychol (Leipz)*. 1987;-39(6):356-361.

WMC-21-037:

Delirium ToolBox in a Nursing Home

Ammu Susheela MD, Howdie Eldib MD, Salman Ali MD
Loyola-Macneal Hospital, Marshall School of Medicine,
Hines VA Medical Center

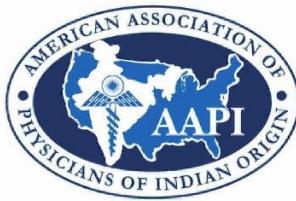
Background: Delirium occurs as a result of acute disorder of attention or cognition. People who are 65 years and older are more prone to delirium. Studies have shown that the incidence of delirium of elderly who got admitted to nursing homes is approximately 60.7%. In 2014 published about a delirium risk modification program and its association with hospital outcomes in a tertiary Boston VA hospital where delirium risk was assessed initially using cognitive impairment, vision impairment, and dehydration. To assess the importance of delirium toolbox in nursing home setting to assess, manage and prevent delirium, we introduced the delirium toolbox to nursing home and created a CPRS template for delirium toolbox.

Methods: Delirium risk was communicated to the providers through electronic medical records and to modify the delirium risk, timely interventions were provided in cognitive stimulation, sensory improvement, and sleep promotion. A stakeholder interview was initially conducted at the Community Living Center (CLC) of nurses, nurse practitioners, physicians, and administrative staff regarding the use of a delirium toolbox template in the CPRS for risk stratification and creating orders for prevention, assessment and management of delirium. A red box was placed in the nursing station containing all the non-pharmacological tools required to prevent delirium.

Results: A sample size of 21 veterans were assessed for a period of 1 month in a nursing home with a mean age of 74 +_9. The delirium measured with 4AT after introduction of delirium toolbox was significantly lower than before introduction. (P <0.05). The morse fall risk score after introduction of delirium toolbox was also significantly lower than before the introduction. (P <0.05). The frailty score before and after introduction of delirium toolbox as well as sleep medication, pain medication, and antipsychotic usage difference was not statistically significant. (P >0.05)

Conclusion: Delirium toolbox enhances patient experiences in CLC. Focusing on preventive non-pharmacological interventions helps to improve patient care in CLC. Delirium toolbox can have positive influence on cognitive rehabilitation and reduce fall risk.

Reference: Perez-Ros P, Martinez-Arnau FM, Baixauli-Alacreu S, Garcia-Gollarte JF, Tarazona Santabalbina F. A predictive model of the prevalence of delirium in elderly subjects admitted to nursing homes. *Endocrine Metab Immune Disord Drug Targets*. 2018;18(4):355-361.



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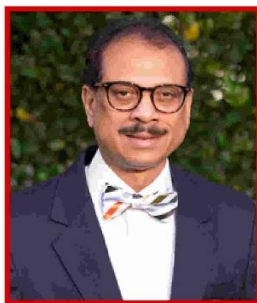


SUSAN R. BAILEY, MD
President, AMA

On May 12, 2021 at 7 pm CST

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