Rs.10

JIMA

Volume 65 (RNI) ◆ Number 01 ◆ JANUARY 2021 ◆ KOLKATA

JOURNAL *Of the* INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in INDEX COPERNICUS INTERNATIONAL Index Medicus

Volume 119 (JIMA) ♦ Number 01 ♦ January 2021 ♦ KOLKATA

Dr ©

Largest Circulated Medical Journal in India

ISSN 0019-5847

91 ST YEAR OF PUBLICATION

Visit us at https: // onlinejima.com

JIMA COMMITTEE 2021

Dr. J.A. Jayalal
National President, IMA

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

Dr. Kakali Sen
Hony.Jt Secretary, HQs.

Dr. Sanjoy Banerjee
Hony.Jt Finance Secretary, HQs.

Dr. Tamonas Chaudhuri
Hony. Editor, JIMA

Dr. Rabindranath Chakraborty
Hony.Associate Editor, JIMA

Dr. Nandini Chakrabarti
Hony. Associate Editor, JIMA

Dr. Jyotirmoy Pal
Hony.Secretary, JIMA

Dr. Kanai Lal Patra
Hony.Asstt.Secretary, JIMA

Dr. Debasish Bhattacharya
Member,JIMA Committee

Dr. Samarendra Kr Basu
Member,JIMA Committee

Dr. Shambo Samrat Samajdar
Member,JIMA Committee

Dr. Udas Ghosh
Member,JIMA Committee

Dr. Rudrajit Pal
Member,JIMA Committee

Dr. Tanuka Mandal
Sub Editor, JIMA

TEAM IMA (2020-21)

National President
Dr. J A Jayalal

Immediate Past National President
Dr. Rajan Sharma

Hony. Secretary General
Dr. Jayesh M. Lele

Hony. Finance Secretary
Dr. Anil Goyal

National Vice President
Dr. Vijaykumar C. Popat

National Vice President
Dr. Ashok Rai

National Vice President
Dr. Shyam Narain Harsh

National Vice President
Dr. Navjot Singh Dahiya

Hony. Joint Secretary
IMA Hqs. (2020-22)
Dr. Anil Aggarwal

Hony. Joint Secretary
IMA Hqs. (2020-22)
Dr. A. K. Israni

Hony. Joint Secretary
IMA Hqs. (2020-22)
Dr. Naresh Chawla

Hony. Joint Secretary
IMA Hqs. stationed at
Calcutta (2020-22)
Dr. Kakali Sen (Mandal)

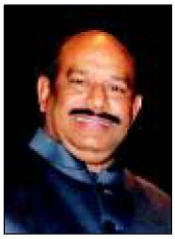
Hony. Asstt. Secretary
IMA Hqs. (2020-22)
Dr. R. K. Sinha

Hony. Asstt. Secretary
IMA Hqs. (2020-22)
Dr. Shitij Bali

Hony. Joint Finance Secretary
IMA Hqs. (2020-22)
Dr. Puneet Dhawan

Hony. Joint. Finance Secretary
IMA HQs. stationed
at Calcutta (2020-22)
Dr. Sanjoy Banerjee

Dean,IMA-CGP (2020-21)
Dr. Natwar Sharda



Vice Dean,IMA CGP (2020-22)
Dr. Janmejaya Mohapatra

Hony. Secretary
IMA CGP (2020-22)
Dr. C. Anbarasu

Hony. Jt. Secretary
IMA CGP (2020-22)
Dr. Jayant Sharma

Hony. Jt. Secretary
IMA CGP (2020-22)
Dr. Prabhat Kr. Shrivastava

Hony. Jt. Secretary
IMA CGP (2020-22)
Dr. Sanjay Dattaraya Patil

Hony. Jt. Secretary
IMA CGP (2020-22)
Dr. Satyajit Borah

Hony. Jt. Secretary
IMA CGP (2020-22)
Dr. S. Rekha

Chairman,
IMA-AMS (2020-21)
Dr. Daggumati Sree Hari Rao

Vice Chairman,
IMA-AMS (2020-22)
Dr. Surya Kant

Hony. Secretary,
IMA-AMS (2020-22)
Dr. Sanjeev Singh Yadav

Hony. Jt. Secretary,
IMA-AMS (2020-22)
Dr. B. Narender Reddy

Hony. Jt. Secretary,
IMA-AMS (2020-22)
Dr. G. Sampath

Editor (Annals),
IMA-AMS (2020-22)
Dr. Srirang Abkari

Director
IMA-AKNSI (2020-21)
Dr. P. K. Rasheed Mohamed

Hony. Executive Secretary
IMA-AKNSI (2020-22)
Dr. Harihar Dixit

Hony. Joint Secretary
IMA-AKNSI (2020-22)
Dr. Dinesh Kumar

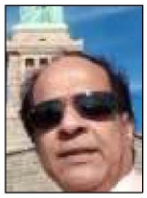
Hony. Joint Secretary
IMA-AKNSI (2020-22)
Dr. Shivendra Kumar Sinha

Hony. Editor-JIMA
(2020-21)
Dr. Tamonas Chaudhuri

Hony. Asso. Editor
JIMA (2020-22)
Dr. Nandini Chakrabarti

Hony. Asso. Editor
JIMA (2020-22)
Dr. Rabindra Nath Chakraborti

Hony. Secretary
JIMA (2020-22)
Dr. Jyotirmoy Pal



Hony. Asstt. Secretary
JIMA (2020-22)
Dr. Kanai Lal Patra

Hony. Editor
Your Health (2020-22)
Dr. Samrendra Kr. Basu

Hony. Asso. Editor
Your Health (2020-22)
Dr. Minakshi Gangopadhyay

Hony. Asso. Editor
Your Health (2020-22)
Dr. Prasanta Kr Bhattacharya

Hony. Secretary
Your Health (2020-22)
Dr. Sarbari Dutta

Hony. Associate Editor
Apka Swasthya (2020-22)
Dr. Ritu Garg

Hony. Associate Editor
Apka Swasthya (2020-22)
Dr. Sudhir Singh

Hony. Secretary
Apka Swasthya (2020-22)
Dr. Manoj Kumar Srivastava

Chairman
IMA HBI (2020-22)
Dr. Sharad Kumar Agarwal

Hony. Secretary.
IMA HBI (2020-22)
Dr. Mangesh Pate

Treasurer
IMA HBI (2020-22)
Dr. Dinesh B. Thakre

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 119 (JIMA)
Number 1
January 2021
KOLKATA
ISSN 0019-5847

Contents

JOURNAL
Of the
INDIAN MEDICAL ASSOCIATION

Volume 119 (JIMA)
Number 1
January 2021
KOLKATA
ISSN 0019-5847

Contents

Prof. Tamonas Chaudhuri
Hony. Editor
MBBS, MS, FAIS, FMAS, FACS, FACRSI (Hony)

Editorial

Are we Marching away from Safety ?

"Health is wealth" is a proverb which has almost been elevated to the status of a hackneyed expression by all plebeians. We speak of it, advocate it to others, with the gravity of Nestor advise our younger generation of it but prefer to remain callous and aloof of it. This gross aloofness has been shaken from the grass root of late by the looming shadow of pandemic. This almost imperceptible diabolic virus (SARS-COV2-19) has steadily percolated into the very fabric of the society and has wreaked havoc shattering our very source of existence. Now, as a repercussion to this violent jerk to our prejudice we have all become unanimously conscious of "LIFE BEING SUPERIOR TO EVERYTHING ON EARTH" and we cannot meddle with life in a childish whim. As like all of us, the Government of India and State Government has shown concern and has implemented preventive measures to check the pandemic. Their effort is laudable, but certain decisions of Central Council of Indian Medicine under the Dept. of Health & Family Welfare, Government of India, can be questioned from the viewpoint of the larger interest of the citizens of India. Let us discuss in detail.

Recently a notification has been released by Central Council of Indian Medicine (CCIM) "These regulations may be called the Indian Medicine Central Council (Post Graduate Ayurveda Education) Amendment Regulations, 2020." The regulation confers the official right to the PG SCHOLARS of Ayurveda stream of medical education to conduct surgery - "During the period of study, the PG scholar of Shalya and Shalakya shall be practically trained to acquaint with as well as to independently perform the following activities so that after completion of his PG degree, he is able to perform the following procedures independently…. MS (AYURVED) SHALYA TANTRA – (GENERAL SURGERY) and MS (AYURVED) SHALAKYA TANTRA (DISEASES OF EYE, EAR, NOSE, THROAT, HEAD, ORO-DENTISTRY.

Friends, for once let us browse the history of surgery in India. Once at the helm, until 18th century, the dexterity of the Indian Surgeons attracted veneration from the Surgeons of the East India Company. Charaka Samhita, Sushruta Samhita

and other variations of surgical practices have branched into various avenues of surgery, right from pediatrics to toxicology to name a few. It is thus an undeniable fact that shalya tantra and shalakya tantra traces its lineage deep into the history of time. However, evolution, modification, research and advanced application of applied science are the key features of human's capability to adopt to the changing and challenging times. The Occidental School of Surgery has however taken lead as compared to the Oriental School in this aspect. Thousands of dedicated scholars round the world have dedicated and are dedicating their full time effort to make surgery less painful, more safe and are trying to lessen the post-operative time of recovery so that the patient may return back to normal life and perform normal day to day chores as efficiently as he used to do before his illness.

May I be allowed to lay down the rigorous and long way that a surgeon needs to traverse before he is allowed to officially work independently. The saga starts like this-- After completion of 10th grade most students determine if they want to choose a track that will lead them to becoming physicians. Following 12th grade, students take part in an entrance exam to gain acceptance into medical school. After completion of medical school, junior doctors take another competitive exam to gain entry into post graduate degree in Surgery which can be followed by super specialty training if needed[2]. The combination of 5½? years (medical school), 3 years (post -graduation) and 2–3 years (super specialty) adds to an approximate total of 10–12 years of training to practice as a Surgeon.

Now let us zero in on the notification of CENTRAL COUNCIL OF INDIAN MEDICINE. Armed with the degree of MS (AYURVED) henceforth the post graduate ayurved scholars will be officially and legally allowed to operate and delve into various branches of surgery as I have mentioned in my introductory paragraph. It's clear that CCIM wants to extend the scope of practical training of PG Scholar of Shalya and Shalakya. As such there is nothing wrong in this that any PG Scholar in any stream of education can be trained for skill within the scope of the subject concerned. A reasonable knowledge is required to acquire that skill. The point to be questioned is something else. As we all know that MS stands for Master of Surgery in modern medical education in Indian medical education system. In this vast country it's next to impossible to identify somebody who designates himself as only MS, as to which stream and school of education he belongs to. Befooling the mass and hoodwinking them under the cover of the acronym MS will be a child's play. Again the competence of the mentors of such budding surgeons from the alternative stream is also questionable. The reluctance of few senior mentors in the mainstream surgery to mould their juniors is quite well known and is a subtle evil yet to be ousted[3]. If this be the situation with the mainstream what can happen to the alternative stream is an open secret.

WHO[4] asserts that they, in unison with the countries of the world, will strive to establish quality healthcare for all people across the globe irrespective of gender, income and so on. As we know quality and expertise are complementary to each other and thus the decision making authorities must consider and reconsider their decisions umpteen number of times before its execution. One of the clearest lessons the pandemic has taught us is the consequences of neglecting our health systems.

1 Central Council of Indian Medicine Notification. The Gazette of India: Extraordinary, Part III – Sec-4. New Delhi, the 19th November 2020.

2 Are C — Surgical Training in India Versus Abroad: What More Needs to be Done?. *Indian J Surg Oncol* 2013; **4(4):** 382. doi:10.1007/s13193-013-0266-3

3 Tandon A — Postgraduate surgical training in India. *Indian J Med Ethics* 2010 Oct-Dec; **7(4):** 264-5. doi: 10.20529/IJME.2010.100. PMID: 22106586.

4 World Health Organisation Spotlight — 10 global health issues to track in 2021. https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021. 24 December 2020.

Insight

Shining India — Dream of A Monk

Jyotirmoy Pal
Hony Secretary, JIMA

Nearly a decade before Independence, in December 1937, while addressing a meeting of the National Academy of Sciences at Calcutta, Jawaharlal Nehru, the then President of INC, revealed his vision and faith in science: "**Politics led me to economics, and this led me inevitably to science and the scientific approach to all our problems and to life itself. It was science alone that could solve these problems of hunger and poverty, illiteracy, superstition otherwise vast resources running to waste.**" Thus the fact that science and modern technology could play a bigger role in building nation was realised by the Congress under Nehru long before Independence.

As India's first Prime Minister, Mr Nehru, on the eve of the country's independence on 14 August 1947 in Constituent Assembly addressed that- "**when the world sleeps, India will awake to life and freedom. We end today a period of ill fortunes and India discovers herself again**."

In next 70 years, India discovered herself as of same potential as Western world in several fields of Technology such as Information Technology, Space research, Defence technology etc. but advancement in medical sciences from Land of Charak and Susruta was need of century and dream of our Country.

Wheels are gearing up, vibrations have been set in motion, Prime Minister called for rising India, Self-reliant India. "**In this decade, we will complete 75 years of our independence. In this decade, we all have to work together with new energy to give impetus to the making of a new India in this century**," he said.

Covid-19 outbreak gave it a push and Covid-19 pandemic came as a curse to an unprepared India. Having a huge population with massive number of immigrants, India's inadequate public health system faced a unique challenge. Indian leadership from Centre to State showed their brave face in this time of crisis. Medical professionals and scientists accepted the situation as opportunity to prove their capability and talent. India largely depends on import from outside for pharmaceutical production and thus diagnostic technology faced crisis of resources at the beginning. But India felt that the Covid-19 crisis needs to be made into a turning point for India's economy and an opportunity to be **"**self-reliant India**"**. Decades ago

Swami Vivekananda wrote, **'The simplest method to be worked upon at present is to induce Indians to use their own produce and get markets for Indian art ware in other countries'**. This path shown by Swami Vivekananda is an inspiration for India in COVID era. Every citizen of India is determined to convert the "**coronavirus crisis into an opportunity"** to build new vibrant India, that can not only save herself but also her neighbour countries as well. Swamiji's India is dreaming to be torchbearer of entire humanity through her wisdom, endeavour, efforts and intellect.

Around a 125 years back, Swami Vivekananda in his speech, which was held in America, told – **"This is your century right now, but coming century is India's century"**. We must strive to make the 21st century to be India's century. We have to consciously make efforts to realise that vision. Swami Vivekananda's concept of "oneness" and "**self reliant**" is what we want today and thus we all would need oneness of the vision, oneness of the mind and effort as has been nicely said through his wise words **"Arise, awake and Stop not, till the goal is achieved"** .

Swami Vivekananda focused on the idea of 'Man Making' and, according to him, through this process of "Man Making" India will arise and awake once more and the ancient mother will be sitting on her throne rejuvenated, more glorious than ever. Swamiji's visit to Chicago in 1893 was one of the most important events in India's history, where Swami Vivekananda represented Indian Darshan, culture and civilisation at the first World Parliament of Religions held at Chicago, USA on 11th of September 1893. In eyes of West, India was considered to be a country of snake charmers, land of superstitions and slaves, which was being ruled by foreign invaders from centuries. Swamiji (1893-97) with his speeches changed the outlook of West towards India. Swamiji says **"If we only adopt Western Ideas, Western language, Western Food, Western Dress, and Western manners, we shall be as strong and powerful as the Western nations; By imitation of other's idea it never become one's own; nothing unless earned, is your own."** We can learn from West but should not imitate their ways

blindly. We have to look across the globe and take ideas but absorb them in our own way.

Dream of self reliance is not new. This dream started from the period of Renaissance in nineteenth century. Self reliance in education, self reliance in health, self reliance if industry, self reliance in thinking. In the 19th and 20th century Indians stood against British exploitation and set up their indigeneous enterprises to make Bharat a self reliant Country. Sir Prafulla Chandra Roy inspired our youths to leave their jobs and to start own business. He established Bengal Chemicals, Jamsetji Tata established Tata Steel at Tatanagar. Dr Radha Govinda Kar made a medical College in Kolkata entirely by contribution from Indians. Against the decision for partition of Bengal made by Lord Curzon in 1905, Rabindra Nath Tagore called for Swadesi movement. As a part of this movement, he urged countrymen to avoid clothes from Manchester and to use Indian self made clothes **–'*khadi*'**. In the movie "***Ghaire Baire***", Satyajit Ray nicely presented this sentiment against the background of that time India. Dream of being Atmanirvar was in heart of Patriotic India even in Colonial Period. Democratic India needs to fulfil the dream of our ancestors who sacrificed their life to make today's Bharat.

The whole world is waiting eagerly for an effective vaccine to fight the coronavirus pandemic. It has not only claimed lives, but also impacted people, both physically and mentally. There are more than 250 vaccines in progress right now, but India is among first 6 countries being close to final approval of vaccine in market. Already India is the proud producer of largest number of Vaccine and supplier to UNICEF and WHO. Export of the vaccine now depends on how a country maintain standard of production and quality control. India have a strong regulatory committee, which meet all criteria laid down by WHO. So also Indian Manufacturers have long tradition of vaccine research and production. This Pandemic has given the opportunity to prove India's capability as a world leader. Immediately after imposing Lockdown, national Task force for Vaccine development and research was formed in April, 2020. ICMR, NIV and Bharat Biotech have proudly taken indigenous project of producing Vaccine, with technology being entirely Indian. On the other hand Zydus Cadila along with Dept of Biotechnology, India also is in progress of making DNA vaccine. There are no licensed vaccines of this kind till now. If this is successful it will put another feather in the cap of Indian Vaccine research. Serum Institute of India already stockpiles 50 million doses and is likely to produce 100 million doses by March 2021. Whereas Bharat Biotech already have 20 million doses in stock and is committed to produce 700 million doses by year end, which is quite unthinkable by any superpower. India also committed to Covax Facillity, an initiative by WHO to provide vaccine to poor and middle income Countries, which is an International commitment.

We are proud with India's capability as innovator and producer of best quality of Vaccine. But there is some concern. There are controversies, criticism on COVAXIN. Some say phase III trial is not completed, some have pointed fingers on inadequate safety data, some say trial reports are not being published in public domain. Question was raised as why government was in such a hurry to give emergency authorization. I agree every citizen have right to put question in a democratic country like India. Safety concern is definitely priority to our leaders. But we have to remember we should not criticize in such a way that may damage international repute of the country. But politically motivated or keeping political mileage in mind or out of Political pull–push glory discovery should not be in lost Bhul Bhulaiya.

Upon approval of Vaccine Dr Samiran Panda, Head Department of Epidemiology and communicable disease ICMR told **"I would say scientifically Covaxin offers much better antigen presentation (and a consequent immune response) than a vaccine developed as a specific part of the (viral) protein."**

We as an Indian should be proud that vaccines, which are being approved, are made in India.

After two of our vaccines received emergency approval, Prime Minister Narendra Modi congratulated the hardworking scientists in India.

"A decisive turning point to strengthen a spirited fight, DCGI granting approval to vaccines of Serum Institute of India & Bharat Biotech accelerates the road to a healthier & a COVID-free nation. Congratulations India. Congratulations to our hardworking scientists & innovators. It would make every Indian proud that the two vaccines that have been given emergency use approval are made in India! This shows the eagerness of our scientific community to fulfil the dream of an Aatmanirbhar Bharat, at the root of which is care and compassion."

World Health Organization (WHO) welcomed India's decision giving emergency use authorization to Covid-19 vaccines. Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia Region said, "**World Health Organization welcomes India's decision giving emergency use authorization to Covid-19 vaccines**."

AS per latest news more than 60 countries representatives have visited vaccine manufacturing site

at Hyderabad. There is lot of appreciation and enthusiasm regarding Indian vaccine in South East and East Asian countries. As a responsible member of Asia, India has a firm commitment to the small countries who are lacking production capability. Some might say there is political intention, there is business intension, but history of Indian trading is to help poor countries. In Indian history there is no evidence of Indian invasion with arms. But, India can conquer hearts of the furthest countries with love, charity and brotherhood. In this century India is following the same pathway what Mahamoti Ashok had set.

The poor Asian countries like Australia and South Africa also shown their interest to procure vaccine from India. This is possible because the Indian technology is able to produce the best quality vaccine with lowest cost. After COVID pandemic India has emerged as a country that is full of possibilities in the race of development. India is ready to take the challenge, with a power that emerges from spirituality of India. "**Trust Yourself**" – was mantra of Swamiji to the youth. If you have faith on yourself, you can achieve. From India every Indian should be Vocal for Local.

So, it is the duty of our countryman, politician, bureaucrats, media person and definitely the leader and members of Indian Medical Association to stand behind the scientists who are dedicating their lives, working day and night to save us. I am sure there they are on the right track and will come out with all transparency and huge success.

We, at Indian Medical Association, appreciate the contributions of all Indian Scientists and Researchers who have relentlessly spent their time in making this dream a success and contributing to develop Self-sufficient India.

— Dr. J A Jayalal, *National President, IMA*

The scientists across India in particular are pressworthy to great extent as in spite of the dreaded pandemic around, have done their best performance in record time.

They have proved beyond doubts that India is always a front-runner in the field of not only vaccine but in research capabilities.

We are proud to have them .

We thank their sheer hard work and consistent efforts in getting the vaccine ready in just under 9 months.

Thank you friends

We owe them a lot.

— Dr. Jayesh M. Lele, *Hony Secretary General, IMA*

Self reliant India, which was actually the dream of Swamiji, can only be achieved through true education, strong public health system, skill development and innovation in science and technology.

During this Covid pandemic, the frontline warriors like doctors, nurses, health workers, scientists, police, corporation workers etc must be congratulated for their relentless effort towards the mankind.

Success in the field of Covid vaccine goes to the scientists of our country.

The fight is not yet over and presently we should follow the saying of Swamiji:

"Arise, awake & stop not, till the goal is reached".

Let's stay focused, safe & healthy.

— Dr. Santanu Sen*, MP, Rajysabha & Past National President, IMA*

Dear JIMA Team,

Congratulations for highlightingthe Covid Vaccine developed in our Nation. Your Shaping of the article looping in the statements of our First Prime Minister, Shri Jawaharlal Nehru ji &Swami Vivekananda, Making India awake till go in achieved is laudable.

Complementing 21st Century as India's Century will Strengthen the hands of our Honourable Prime Minister Shri Narendra Modi ji.

Our Scientists& Innovators of Serum Institute of India& Bharat Biotech made true the dream of our Honourable PMji, " Make in India, to a Self Reliant India"

The Vaccine invented by our Indian Scientists& approved by DCGI & ICMR has received illustrative appreciations from WHO & Global Healthcare Leaders. Our India Developed vaccine is going Global to serve the Humanity. Earlier we were dependent on other Nation for our needs; now the situation is reversed.

We, API,the largest Professional body of Physician in India, Congratulate, appreciate &salute the Scientists & Innovators of Covid Vaccine India.

Best Wishes,

— Dr S Arulrhaj, *National President API*

JAI HIND.....VANDE MATARAM

Review Article

Repurposing Mefenamic Acid in the Management of COVID-19

K K Aggarwal[1], Yeh Woei Chong, Rajan Sharma, Marthanda Pillai, Ravi Naidu, Alvin Yee-Shing Chan, Marie Uzawa Urabe, Debora Cavalcanti, Prakash Budhathoky, Qalsar Sajjad, Russel D'Souza, N Ganabaskaran, Md Jamaluddin Chowdhary, Prakash, R V Asokan, Ramesh K Datta, Jayakrishnan Alapet, V K Goel, Brijendra Prakash, Shashank Joshi, Ashok Gupta, Suneela Garg, Alex Thomas, D R Rai, J A Jayalal, P N Arora, K Kalra, A K Aggarwal, Anita Chakravarti, Atul Pandya, Shantanu Tripathi, Bejon Mishra, T S Jain, Anil Pachnekar, Shivkumar S Utture, Ketan Mehta, R P Pareek, Alok P Nachane, Ambanna Gowda, Shilpa Karande

With the growing understanding of coronavirus disease-2019 (COVID-19) pathogenesis, different therapeutic targets are being considered for the management of COVID-19. The development of new drugs is a time-consuming process; hence, many drugs acting on similar therapeutic targets/sites in the COVID-19 treatment are repurposed in COVID-19.

In this article, an expert panel deliberated on the existing evidence on the immunopathogenesis, therapeutic targets under consideration for treatment of COVID-19, and the place of mefenamic acid in the therapy landscape of COVID-19. The expert panel has also provided recommendations regarding the dose and regimen of mefenamic acid in different phases of the COVID-19 disease.

[*J Indian Med Assoc* 2021; **119(1):** 16-23]

Key words **: Mefenamic acid, COVID-19, repurposed drugs, NRP3 inflammasome.**

In the coronavirus disease 2019 (COVID-19) pandemic scenario, there are no specific agents against severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), while COVID-19 continues to be a public health emergency affecting millions of people across the globe. Given this, experts have identified and recommended some therapies such as a combination of two HIV drugs, antimalarial drugs, and an experimental antiviral compound remdesivir to be used in the management of COVID-19[1]. Even though the search for new agents is continuing, the demands for new effective agents and therapies is enormous. Hence, several drugs already available for other indications have undergone clinical trials to repurpose against COVID-19. With increasing knowledge about the pathogenicity of the disease, different therapeutic targets are being considered, and drugs acting on thevirus-related or host-related targets are repurposed for COVID-19[2]. The SARS-CoV-2 infection has aggressive inflammatory responses strongly implicated in the resulting damage to the airways and several other body organs. Here, we have considered repurposing mefenamic acid in COVID-19 for its antipyretic, anti-inflammatory, and antiviral properties.

Editor's Comment :

- **Many old drugs are being repurposed for Covid-19 with varying Success.**
- **Mefenamic acid, an NSAID, inhibits the NRP3 inflammasome.**
- **This can theoretically inhibit cytokine over activation.**
- **This is also useful for Post-Covid Myalgia**

Methodology :

The present review examines the existing evidence on the immunopathogenesis of COVID-19 and the role of mefenamic acid in its management. The review presents evidence-based and clinical experience-based recommendations on the use of mefenamic acid in the management of COVID-19.

To inform the highest possible evidence base for the use of mefenamic acid in COVID-19, a systematic review of the literature was conducted on PubMed, Cochrane database, and Google Scholar. Existing guidelines, meta-analysis, systematic reviews, randomized controlled trials (RCTs), non-RCT studies, and experimental studies relating to the benefits of mefenamic acid and the immunopathogenesis of COVID-19 were searched, scanned, selected, and reviewed. Only articles in English and COVID-19, experimental, clinical studies, or review on mefenamic

[1]MBBS, MD, Recipient of Padma Shri, Vishwa Hindi Samman, National Science Communication Award and Dr B C Roy National Award, Past National President IMA, Honorary Secretary General IMA, New Delhi 48

Received on : 28/07/2020
Accepted on : 12/09/2020

acid were included. Articles in other foreign languages and focusing on other respiratory disorders were excluded from the selection.

Recommendations for the use of mefenamic acid are based on the available evidence and preliminary discussions among expert groups. Several rounds of discussions ensued with the Confederation of Medical Associations of Asia and Oceania (CMAAO) group of experts, the Indian Medical Association (IMA) panel, and the committee of experts, including clinicians treating or undertaking research in COVID-19 management, which was specially formed to delve into the available evidence and relevant clinical experience on mefenamic acid.

The expert panel then discussed the recommendations formulated above, put forth in this article. Where there was little or no evidence, the panel relied on logical empiricism and consensus to generate the recommendations about the rational use of mefenamic acid in the management of COVID-19.

Immunopathophysiology of COVID-19 :

The virus —

The virus responsible for COVID-19 disease belongs to the family Coronaviridae. Inhumans, most coronavirus infections lead to mild respiratory symptoms and may be attributed to causing almost 20-30% of common colds[3]. The virus has too high transmissibility and a degree of lethality comparatively lesser than the SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus). However, the situation is currently evolving, and the degree of lethality is yet to be established globally[4].

Coronaviruses possess single-stranded positive RNA, spike-S, membrane-M, and envelope-E proteins in the virus envelope. Nucleocapsid-N is present inside the virion that covers the RNA. From 5' to 3', genes for the replicases ORF1a,b are located on the viral genome,occupying two-thirds of the genome, and code for the polyproteins pp1a and pp1b. Towards the 3' end, the genes for structural proteins S,E,M, and N are present[4].

Protein S contains the receptor-binding domain for the ligand on the host cell membrane and the epitopes recognized by T and B cells, which trigger antibodies' production. The primary receptor for the SARS-CoV-2 on the host membrane is the angiotensin-converting enzyme 2 (ACE2). It is present on the membrane of many cells, including type I and II pneumocytes, small intestine enterocytes, kidney proximal tubule cells, the endothelial cells of arteries and veins, and the arterial smooth muscle. Receptor-binding domain essential for ACE2 binding mobilises conformational changes on S leading to cleavage of S1 and S2 proteins, mediated by the transmembrane *serine protease* 2 (TMPRSS2), enabling S2 to facilitate the fusion of the virus envelope with the cell membrane thus permitting viral entry into the cytoplasm of the host cell. Inside the cell, viral RNA serves as a template for the translation of the polyprotein pp1a and pp1b that are split into 5-16 nonstructural proteins (nsp2-nsp9), leading to a reshuffling of the membranes to form the vesicles where viral replication and transcription complexes are secured. The virions are gathered in the ER-Golgi, and the secretory pathways eventually release mature virions[4].

The Innate Immune Response :

During the SARS-CoV-2 infection, the virus is recognized by pattern recognition receptors (PRR) such as toll-like receptor (TLR)-7 and TLR8, retinoic acid-inducible gene-I-like receptors (RLRs) and NOD (nucleotide binding and oligomerization domain)-like receptor (NLR) expressed by epithelial cells as well as by local cells of the innate immune response, such as alveolar macrophages. After binding to the ligand, PRRs recruit adaptor proteins activating crucial downstream transcription factors, including interferon regulatory factor (IRF), nuclear factor kappa B (NF-κB), and AP-1 leading to the production of type I and typeIII antiviral interferons (IFNs) and different chemokines[5]. These chemokines attract more innate response cells, polymorphonuclear leukocytes, monocytes, NK cells, dendritic cells, which also produce chemokines. SARS-CoV-2-induced five cytokines: IL-6, MCP1, CXCL1, CXCL5, and CXCL10/IP10. SARS-CoV-2 induces a specific signature featured by decreased IFN-I and IFN-III responses and significant induction of multiple pro-inflammatory chemokines, IL-1β, IL-6, tumor necrosis factor (TNF-α), and IL1RA. These findings have been supported by the increased serum levels of these cytokines in COVID-19 patients[4].

The Adaptive Immune Response :

The transition from innate to adaptive response is crucial because, at this juncture, the immune regulatory events will lead to the development of either a protective immune response or an exacerbated inflammatory response. The protective response is T cell-dependent, with CD4 helping B cells help in producing specific neutralizing antibodies and cytotoxic CD8 cells eliminate infected cells. It has been found that in COVID-19, 80% of the infiltrating cells are CD8[6]. In the case of a dysfunctional response, an exacerbated inflammatory response leads to a cytokine

storm, clinically manifested by severe acute respiratory distress syndrome (ARDS) and systemic results like disseminated intravascular coagulation[4]. The disease is hypothesized to be divided into two phases; an early phase dependent on viral replication and a later viral-independent, immune-dependent phase accompanied by an exacerbated inflammatory component.

Prostaglandins Involvement :

Arachidonic acid (AA) possesses potent antimicrobial activity via leakage and lysis of microbial cell membranes, viral envelope disruption, amino acid transportation, inhibition of respiration, and uncoupling of oxidative phosphorylation[7]. It is also suggested that reduced concentration of AA may be the causative factor for the absence of inhibition of SARS-CoV-2 replication in COVID-19 patients[8]. On the contrary, a decrease of AA levels has also been observed in COVID-19 patients, who could be attributed to the conversion of AA into prostaglandins via up-regulated gene expression of cyclooxygenase (COX)-1, COX-2, and PTGES3 and increased PGE2levels. Also, cytosolic phospholipase A2α (cPLA$_2\alpha$) genes,which are highly expressed in the endothelial and epithelial cells of the human lung, are up-regulated in COVID-19 patients[9].

Infection with SARS-CoV-2 ligates various pathogen recognition receptors such as TLR and/or RLRs and triggers transcription factors such as IFN regulatory factor 3 (IRF3) and NF-κB that are responsible for the expression of type I and III IFNs and pro-inflammatory mediators, including TNF-α, IL-6, and PGE2, respectively. NF-κB is the vital transcription factor responsible for the induction of pro-inflammatory cytokines. Activation of NF-κB can stimulate gene expression of inducible COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) in many cell types bringing about the production of COX-2-dependent PGE2.This PGE2acts autocrinally and/or paracrinally on NF-κB stimulation to expand pro-inflammatory cytokines and chemokines through the E-type prostanoid receptor (EP)-2 receptors. In humans, PGE2 promotes IL-1β-dependent production of IL-6, macrophage colony-stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF) from human fibroblasts via EP4 receptors. It also enhances induction of IL-6 and other pro-inflammatory cytokines upon many stimuli in monocytes, macrophages, fibroblasts, and airway epithelial cells through both EP2 and EP4 receptors. Besides, IL-6 also up-regulates COX-2 gene expression and increases PGE2 production, working together for normalized production of other inflammatory factors such as MMP9. PGE2 can also trigger IL-6 production in a paracrine way[10].

NLRP3 Inflammasome :

It has been observed that several external and internal stimuli, including viral RNA (E protein and ORF3a of SARS-CoV), trigger the activation of NLRP3 inflammasome through mechanisms including formation of pores with ion redistribution and lysosomal disruption, leading to inflammation and associated cell death. Once NLRP3is activated, procaspase-1 is converted to the active effector protease caspase-1, which leads to cleavage and maturation of pro-inflammatory cytokines like pro-IL-1β into its active form IL-1β and that of IL-18. These pro-inflammatory cytokines stimulate a cascade of other downstreammediators of inflammation, including IL-6, TNF-α, prostaglandins, and leukotrienes[11].

Abnormal activation and triggered cascade of downstream mediators may lead to pathological tissue injury during infection, as is s-αeen in the case of SARS-CoV-2 infection[12]. Infection with SARS-CoV notably induces a storm of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, all of which play a vital role in the progression of tissue inflammation causing ARDS and eventually leads to death[13]. Based on this strong inflammatoryability of the NLRP3 inflammasome, it forms an important target in the treatment strategy of COVID-19.

Cytokine Storm and COVID-19 :

Mortality in COVID-19 patients has been associated with the presence of the “cytokine storm” induced by the virusand the hyper-inflammatory immune response of the host. Excessive formation of pro-inflammatory cytokines causes aggravation of ARDSand widespread tissue damage resulting in multi-organ failure and death. The cytokine storm in COVID-19 is related directly to lung injury, multi-organ failure, and unfavorable prognosis of severe COVID-19. Three of the most critical pro-inflammatory cytokines of the innate immune response are IL-1β, TNF-α, and IL-6. These cytokines are produced by tissue macrophages, mast cells, endothelial and epithelial cells during the innate immune response. A sudden acute boost in circulating levels of different pro-inflammatory cytokines (such as IL-6, IL-1β, TNF-α, and IFN). The increase in cytokine levels leads to the recruitment of several immune cells like macrophages, neutrophils, and T cells from blood circulation into the infection site with the destructive effects on human tissue resulting from the destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse

alveolar damage, multi-organ failure, and eventual death. Lung injury is a severe manifestation of the cytokine storm that can progress into ARDS. Given the above discussion, the early detection and prompt treatment can lead to a better outcome of COVID-19[14].

Fever in COVID-19 :

The first presentation of fever during the first week in COVID-19, during the viral phase of the illness, is probably a manifestation of the body's immune reaction to the replication of the virus to enhance immunity. However, when the infection does not resolve indue course, it leads to a complicated disease process stimulated by the viral activated state of dysregulated inflammation referred to as cytokine storm or secondary hemophagolymphocytosis, foreshadowed by chronic fever[15]. In these cases, where fever occurs due to severe inflammation, it may be counter productive. Here, fever is not beneficial at this stage, as it may promote further inflammation and non-advantageous immune activation. Hence, fever may have a differential impact on the prognosis during the viral and inflammatory stage of the disease marking the use of antipyretics in different stages of COVID-19 infection[16].

Post-COVID Myalgia :

Myalgia reflects generalised inflammation and cytokine response and may even be the onset symptom in 36% of patients with COVID-19. It has been noted that common myalgia caused by COVID-19 is more prolongedand severe when compared with other viral infections and may be unresponsive to traditional painkillers. It is also seen that as the viral load is reduced with treatment, muscle pain may subsequently reduce[17].

As the acute COVID-19 infection has been alleviated, some patients experience long-term adverse effects similar to those of chronic fatigue syndrome or myalgic encephalomyelitis with symptoms including persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep. Due to the build-up of cytokines in the central nervous system maybe the cause of post-viral symptoms because of the pro-inflammatory cytokines passing through the blood-brain barrier in circumventricular organs such as the hypothalamus, leading to autonomic dysfunction[18].

Repurposing Mefenamic Acid in COVID-19 Management :

Antiviral Activity —

Angiotensin-converting enzyme 2 is the host cell receptor for the S protein of SARS-CoV-2, and TMPRSS2 is required for S protein priming of SARS-CoV-2. Their inhibition may prevent cell entry of the SARS-CoV-2[19]. Mefenamic acid inhibits the formation of M28, thereby acting as a protease inhibitor. The inhibition of the protease has been reported to be of significance in the treatment of COVID-19[20].

Earlier studies have also shown that mefenamic acid possesses antiviral activity. The inhibitory effect of mefenamic acid against RNA viruses has been assessed as 90% at a concentration of 30 μM[21]. Mefenamic acid is thus a drug with protease inhibitory action in conjunction with other antiviral drugs or even on its own[22].

A study was performed to assess the potential antiviral activity of nonsteroidal anti-inflammatory drugs (NSAIDs) under the assumption that active compounds with potential antiviral and anti-inflammatory activities could be used in human subjects to treat chikungunya virus (CHIKV) infections. The results showed that mefenamic acid possessed potential antiviral activity both *in vitro* and *in vivo*. A better activity was reported when it was administered in combination with the common antiviral drug, ribavirin. The combination of the antiviral and anti-inflammatory effects of mefenamic acid was beneficial in significantly reducing the pathological signs. The viral titer quantification revealed in the blood of CHIKV-infected mice through the plaque formation assay showed that treatment with the combination of ribavirin and mefenamic acid exhibited a 6.5-fold reduction compared with untreated controls. There are suggestions that these findings might lead to the use of combination against other viral infections[23].

An older study has demonstrated that mefenamic acid, along with doxycycline, had antiviral activity. The inhibitory effect of mefenamic acid against RNA viruses is estimated to be 90% at a concentration of 30 μM[21].

Anti-inflammatory and antipyretic activity :

Cyclooxygenase Inhibition —

There are two COX isoforms, COX-1 and COX-2, which catalyse the first two steps of prostaglandin biosynthesis from AA and are the pharmacological targets of NSAIDs. Mefenamic acid depicts selective inhibition of 2-arachidonylglycerol (2-AG) oxygenation by COX-2[24].

Action on Prostaglandins :

PGE2 has multifaceted effects on the modulation of T-cell responses. PGE2 suppresses T-cell receptor-dependent T-cell activation and proliferation via EP2/EP4 receptor-mediated cyclic adenosine 3',5' -monophosphate (cAMP)-PKA (protein kinase A) pathway, but this suppressive effect is weakened by

enhancing CD28 co-stimulation through augmentation of phosphatidylinositol 3 kinase (PI3K) signalling. Following SARS-CoV-2 infection, the pathway related to CD28 signalling in T helper cells was significantly down-regulated, while the PKA pathway and PGE2 biosynthesis pathway were significantly up-regulated. Thus, PGE2–cAMP-PKA signalling is likely to inhibit antigen-dependent activation of antiviral T-cell responses in COVID-19 patients. On this basis, the use of NSAIDs by inhibiting endogenous PGE2 production may enhance antiviral T-cell responses in COVID-19 patients[10]. The fenamates (like mefenamic acid) possess a dual inhibitory action; they rapidly neutralize the effects of preformed prostaglandins as well as prevent the continuing synthesis of prostaglandins by inhibiting the synthetase enzyme system[25].

Action on NLRP3 Inflammasome :

Fenamate NSAIDs (mefenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1β release by blocking the membrane volume regulated anion [chloride] channel (VRAC). This blockade acts independently of its COX-mediated anti-inflammatory activity. It has also been established that there is a synergy between inhibitors in inflammatory pathways to bring about different levels of inhibition much more than observed singly[26]. Hence, molecules such as mefenamic acid, which modulate several points in a pathway, have an increased probability of leading to enhanced protective effects as compared to molecules that act on a single target[27]. This also allows them to confer greater efficacy at lower doses. Another advantage of this blockade is that the use of fenamates would avoid compromising NLRC4 or AIM2 inflammasome-dependent host responses to infection[26].

In the SARS-CoV-2 infection, there is a role of NLRP3 inflammasome inhibitors in terms of the inflammatory manifestations; this draws attention towards mefenamic acid[22].

Mefenamic Acid and Other NSAIDs :

Studies demonstrated that unlike other NSAIDs, fenamates (mefenamic acid, flufenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1β release[11]. In a study, it was shown that indomethacin led to small intestinal damage through NLRP3 inflammasome-derived IL-1β via TLR4- and P2X7-dependent signalling pathways[28]. Paracetamol overdose triggers the release of danger-associated molecular proteins (DAMPs), which bring about transcriptional activation of pro-inflammatory cytokines in macrophages through TLRs and inflammasome activation, causing liver damage[29]. Other than one study which showed that naproxen in low doses inhibits NFκB activity[30], there was no other clinical study mentioning the association of naproxen with NLRP3 inflammasome inhibition.

NSAIDs block prostaglandin and may exhibit antiplatelet effects and hence are clinically useful in the management of COVID-19[10]. Mefenamic acid possesses a dual inhibitory effect of neutralising the effects of prostaglandinas well as inhibiting its synthesis[25]. Fenamates have a direct inhibitory effect on PGE receptor binding at the usual therapeutic

5 important points regarding Mefenamic Acid :

1. Mefenamic acid inhibits cyclooxygenase (COX-1 and COX-2) and has analgesic, anti-inflammatory, and antipyretic properties, as it is a potent inhibitor of prostaglandin synthesis.

2. Mefenamic acid is indicated for

(a) mild to moderate pain in patients = 14 years of age (when therapy will not exceed one week)

(b) For treatment of primary dysmenorrhea

3. This drug should not be started in back ground of thrombotic events (post MI, post CABG, stroke) and patients with GI Ulcer, bleeding. Need to aware of the risk factors like hepatotoxicity, hypertension, acute kidney injury, hyperkalemia, heart failure, pedal edema, skin reactions and anaphylaxis while using mefenamic acid.

4. Known hypersensitivity, History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs, In the setting of coronary artery bypass graft (CABG) surgery - mefenamic acid is strictly contraindicated.

5. While using to treat acute pain in adults and adolescents ≥14 years of age, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours as needed, usually not to exceed one week.

For the treatment of primary dysmenorrhea, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours, given orally, starting with the onset of bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days.

dosage. Other prostaglandin synthetase inhibitors have not shown such a dual mode of action, and no effect was reported for acetylsalicylic acid[31].

Indomethacin is a potent nonselective COX inhibitor that was widely used as an anti-inflammatory medication. However, it has become unfavorable because of its tendency toward adverse events compared with other commercially available NSAIDs. Owing to the adverse events, its indication and duration of use are limited[32]. It is already mentioned that indomethacin use also led to the damage of the small intestine along with the promotion of caspase-1 and IL-1β maturation underlying the role of IL-1β in indomethacin-induced enteropathy. However, IL-18 activated by inflammasomes with pro-inflammatory activities was not activated[28]. Contrary to this, another study using a mice model showed that indomethacin could protect pancreatic acinar cells from injury by inhibiting the NLRP3 inflammasome pathway and hence reduce the severity of severe acute pancreatitis[33]. Such contradictory results have created ambiguity around the role of indomethacin in NLRP3 inflammasome activation, and more research is required to comprehend its role in the NLRP3 pathway. Currently, there are no reports suggesting the action of ibuprofen or diclofenac on the NLRP3 inflammasome action.

Acetaminophen (paracetamol) is in use as an antipyretic agent for a long time. It reduces prostaglandin synthesis in the brain. However, it does not inhibit prostaglandin synthesis in the periphery and hence does not have any anti-inflammatory action. Along with potential side effects, it might also lead to severe hypersensitivity reactions. Even though considered a dependable antipyretic, there have been reports where paracetamol has failed to control fever leading to the search for other antipyretics. Paracetamol and NSAIDs have essential differences, including the former's weak inflammatory effects and its generally poor ability to inhibit COX in the presence of a high concentration of peroxides as are found at sites of inflammation[32]. Hepatic injury and subsequent hepatic failure due to both intentional and nonintentional overdose of paracetamol have affected patients for decades. It is considered to be one of the most common pharmaceutical products to cause drug-induced liver injury[34]. Acetaminophen has also displayed hepatotoxicity in many combination medications; hence caution is needed with its use[32].

Table 1 — *Action of Different NSAIDs on the Various Immunopathogenesis of COVID-19*

Cytokine	Paracetamol	Naproxen	Indomethacin	Nimesulide	Mefenamic acid
IL-1β		+			++
IL-6		+	+	+	+++
IL-18	×	×	×	×	+
TNF-α					++
NLRP3	×	×	Ambiguity	×	✓
Viral load	×	Prevents viral entry & replication	Inhibits viral replication at a higher dosage	×	Inhibits the serine protease and viral replication

Nimesulide also possesses analgesic and antipyretic properties and has comparable efficacy to naproxen, acetylsalicylic acid, paracetamol, and mefenamic acid; however, it is associated with fulminant hepatitis[35].

As is clear from the discussion in previous sections, mefenamic acid is a potent COX inhibitor and causes both central and peripheral analgesic action. In a study comparing the efficacy and safety of paracetamol and mefenamic acid in the treatment of fever, it was reported that both paracetamol and mefenamic acid were effective antipyretic drugs. In the study findings, the body temperature reduced more in the mefenamic acid compared with the paracetamol group, six hours after the treatment. Also, the fall in temperature at 1 hour was better in the mefenamic acid group. Mefenamic acid thus exhibited a highly significant reduction in the body temperature baseline to the sixth hour compared with paracetamol in pediatric patients with fever ($p<0.01$)[35]. Comparable results were seen in a previous study, which demonstrated that mefenamic acid was more potent antipyretics than paracetamol[36]. Based on the above evidence, Table 1 had been formulated to depict the effect of different NSAIDs on different aspects of the immunopathogenesis of COVID-19.

Recommendations of the Expert Panel :

1. COVID-19 can be classified into two phases: a viral phase and the second immune-inflammatory phase. Since there are no treatments for the disease currently, several pre-existing drugs with antiviral action or action on different regulators of the inflammatory phase can be repurposed in the management of COVID-19.

2. While both NSAIDs and acetaminophen

(paracetamol) can be used as antipyretic agents in the management of fever, given the understanding of the fever in COVID-19, it is important to note that paracetamol does not possess the same anti-inflammatory features that NSAIDs possess. Experts also opined that anti-inflammatory drugs like ibuprofen could act as an aggravating factor for the infection.

3. Mefenamic acid with established antipyretic action is one such NSAID that can be used safely right from the first day of infection.

4. Mefenamic acid can be used at any stage of COVID-19, contradictory to steroids,which should be avoided during the viremic phase of the infection.

5. An additional advantage of mefenamic acid is that it possesses anti-inflammatory, analgesic, and antiviral effects as well. When used in the inflammatory phase of the disease, mefenamic acid acts on the NLRP3 inflammasome and inhibits it, thereby reducing IL-1β, IL-18, IL-6, and TNF-α.

6. In individuals with persistently high C-reactive protein (CRP) (persistent inflammation), mefenamic acid can be given in a dose of 500 mg thrice a day for long-term (up to 3 months), in post-COVID syndrome along with oral anticoagulants to break the cycle of inflammation and inflammation begetting thrombosis.

7. Mefenamic acid possesses antipyretic action for both the thermodysregulation of the hypothalamus and fever associated with cytokine storm.

8. Mefenamic acid is effective in a fever, not responding to paracetamol. It also possesses antipyretic action in those cases where fever is not responding to steroids.

The recommendations for the use of mefenamic acid in the management of COVID-19 adult patients are:

1. 500 mg mefenamic acid 2-3 times a day for 7-10 days

2. In case of high CRP levels persisting in the inflammatory phase, may continue with mefenamic acid (500 mg, three times a day) for up to three months or till the CRP value optimize, for managing inflammation.

3. In post-COVID syndrome, mefenamic acid may be considered in a dose of 500 mg, times a day for up to three months.

Precautions :

In the case of patients with estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73m^2, mefenamic acid should be temporarily discontinued, while in those with eGFR<30 mL/min/1.73m^2, mefenamic acid should be avoided. When used in elderly or geriatric patients, caution should be exercised in patients above 65 years of age; in patients over 75 years or receiving concomitant oral/parenteral corticosteroids, anticoagulants or antiplatelets has increased risk of gastrointestinal bleed; or if transaminase elevation is increased over 2-3 folds. Mefenamic acid is pregnancy category C; it should only be used with caution if benefits outweigh risks. However, it should be avoided in the third trimester. Mefenamic acid is a safe antipyretic in children; however, in COVID-19, it is not advisable in children under 14 years of age due to lack of clinical evidence.

Conclusion :

Blocking the viral entry and replication and inhibiting the cytokine storm via blocking various immune-inflammatory pathways are essential therapeutic targets in COVID-19 treatment. IL-1β, IL-6, and TNF-α are the three most important pro-inflammatory markers leading to tissue inflammation, ARDS, and eventual death.

Mefenamic acid is an NSAID with antiviral, anti-inflammatory, analgesic, and antipyretic activities. It is a known COX-inhibitor,which also has an inhibitory action on the NLRP3 inflammasome and additionally inhibits the serine proteases of the virus.It has shown potent action in blocking all the three implicated pro-inflammatory biomarkers responsible for causing cytokine storm.

Various members from the expert panel shared their anecdotal experience on the effectiveness of mefenamic acid as an antipyretic, analgesic, and anti-inflammatory agent in the management of COVID-19 patients.Thus, the expert panel has recommended the use of mefenamic acid (500 mg, thrice a day) in the management of COVID-19 in adults. However, more extensive clinical trials are warranted to establish the samein the management of COVID-19.

References

1 Harrison C — Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol* 2020; **38(4):** 379-81.

2 Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK — Drug repurposing approach to fight COVID-19. *Pharmacol Rep* 2020: 1-30.

3 Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G — Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress* 2020; **4(4):** 66-75.

4 García LF — Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol* 2020; **11:** 1441.

5 Hur S — Double-stranded RNA sensors and modulators in innate immunity. *Annu Rev Immunol* 2019; **37(1):** 349-75.

6 Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, *et al* — Coronavirus infections and immune responses. *J Med Virol.* 2020; **92(4):** 424-32.

7 Das UN — Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: a review. *J Adv Res* 2018; **11:** 57-66.

8 Das UN % Can bioactive lipids inactivate coronavirus (COVID-19)? *Arc Med Res* 2020; **51(3)**: 282-6.
9 Yan Q, Li P, Ye X, Huang X, Mo X, Wang Q, *et al* — Longitudinal peripheral blood transcriptional analysis of COVID-19 patients captures disease progression and reveals potential biomarkers. *medRxiv.* Published online May 8, 2020:2020.05.05.20091355.
10 Robb CT, Goepp M, Rossi AG, Yao C — Non-steroidal anti-inflammatory drugs, prostaglandins, and COVID-19. *Br J Pharmacol* 2020; **177(21):** 4899-920.
11 Shah A % Novel coronavirus-induced NLRP3 inflammasome activation: a potential drug target in the treatment of COVID-19. *Front Immunol* 2020; **11:** 1021.
12 da Costa LS, Outlioua A, Anginot A, Akarid K, Arnoult D — RNA viruses promote activation of the NLRP3 inflammasome through cytopathogenic effect-induced potassium efflux. *Cell Death Dis* 2019; **10(5):** 346.
13 Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Castaño-Rodriguez C, Fernandez-Delgado R, *et al* — Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology* 2015; **485:** 330-9.
14 Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R — The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020; **11:** 1446.
15 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ — COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020; **395(10229):** 1033-4.
16 Gul MH, Htun ZM, Inayat A — Role of fever and ambient temperature in COVID-19. *Expert Rev of Respir Med*. Published online September 9, 2020: 1-3.
17 Kucuk A, Cumhur Cure M, Cure E — Can COVID-19 cause myalgia with a completely different mechanism? A hypothesis. *Clin Rheumatol* 2020; **39(7):** 2103-4.
18 Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A — Into the looking glass: Post-viral syndrome post-COVID-19. *Medical Hypotheses* 2020; **144:** 110055.
19 McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C — Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res* 2020; **157:** 104859.
20 Ghosal A, Yuan Y, Tong W, Su AD, Gu C, Chowdhury SK, *et al* — Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. *Drug Metab Dispos* 2011; **39(3):** 510-21.
21 Inglot AD — Comparison of the antiviral activity in vitro of some non-steroidal anti-inflammatory drugs. *J Gen Virol.* 1969;**4(2):** 203-14.
22 Pareek R — Use of mefenamic acid as a supportive treatment of COVID-19: A repurposing drug. *Int J Sci Res* 2020; **9(6):** 69-73.
23 Rothan HA, Bahrani H, Abdulrahman AY, Mohamed Z, Teoh TC, Othman S, *et al* — Mefenamic acid in combination with ribavirin shows significant effects in reducing chikungunya virus infection in vitro and in vivo. *Antiviral Res* 2016; **127:** 50-6.
24 Prusakiewicz JJ, Duggan KC, Rouzer CA, Marnett LJ — Differential sensitivity and mechanism of inhibition of COX-2 oxygenation of arachidonic acid and 2-arachidonoylglycerol by ibuprofen and mefenamic acid. *Biochemistry* 2009; **48(31):** 7353-5.
25 Jakubowicz DL, Wood C — The use of the prostaglandin synthetase inhibitor mefenamic acid in the treatment of menorrhagia. *Aust New Zealand J Obstet Gynaecol* 1978; **18(2):** 135-8.
26 Daniels MJ, Rivers-Auty J, Schilling T, Spencer NG, Watremez W, Fasolino V, *et al* — Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models. *Nat Commun* 2016; **7:** 12504.
27 Small BG, McColl BW, Allmendinger R, Pahle J, López-Castejón G, Rothwell NJ, *et al* — Efficient discovery of anti-inflammatory small-molecule combinations using evolutionary computing. *Nat Chem Biol* 2011; **7(12):** 902-8.
28 Higashimori A, Watanabe T, Nadatani Y,Takeda S, Otani K, Tanigawa T, *et al* — Mechanisms of NLRP3 inflammasome activation and its role in NSAID-induced enteropathy. *Mucosal Immunol*. 2016; **9(3):** 659-68.
29 Woolbright BL, Jaeschke H — Role of the inflammasome in acetaminophen-induced liver injury and acute liver failure. *J Hepatol*. 2017; **66(4):** 836-48.
30 Hsueh MF, Bolognesi MP, Wellman SS, Kraus VB — Anti-inflammatory effects of naproxen sodium on human osteoarthritis synovial fluid immune cells. *Osteoarth Cartil* 2020; **28(5):** 639-45.
31 Rees MC, Cañete-Solér R, López Bernal A, Turnbull AC — Effect of fenamates on prostaglandin E receptor binding. *Lancet* 1988; **2(8610):** 541-2
32 William BS — Nonopioid analgesics. In: *Essentials of Pain Medicine*. 2018:457-68. Accessed October 16, 2020. https://sci-hub.st/10.1016/B978-0-323-40196-8.00051-6
33 Lu G, Pan Y, Kayoumu A, Zhang L, Yin T, Tong Z, *et al* — Indomethacin inhabits the NLRP3 inflammasome pathway and protects severe acute pancreatitis in mice. *BiochemBiophys Res Commun* 2017; **493(1):** 827-32.
34 Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N — Acetaminophen-induced hepatotoxicity: A comprehensive update. *J Clin Transl Hepatol* 2016; **4(2):** 131-42.
35 Rahul K, Aishwarya S, Chavva AK — Evaluation of efficacy and tolerability of acetaminophen (paracetamol) and mefenamic acid as antipyretic in pediatric patients with febrile illness: A comparative study. *Int J Med Res Health Sci* 2013; **2(1):** 23-9.
36 Keinänen S, Similä S, Kouvalainen K — Oral antipyretic therapy: Evaluation of the N-aryl-anthranilic acid derivatives mefenamic acid, tolfenamic acid and flufenamic acid. *Eur J Clin Pharmacol*. 1978;**13(5):** 331-4.

Review Article

Classical and Molecular Virology in the Context of SARS-CoV-2

Shailesh D Pawar[1], Babasaheb V Tandale[2], Deeksha S Tare[3], Sachin S Keng[4], Sadhana S Kode[5], Priya Abraham[6]

Diagnostic virology has evolved as a discipline from being confined to hospital laboratories to dedicated state-of-the art research facilities around the world, working on different aspects of diagnosis and research on viral diseases. As the world struggles with the ongoing pandemic of Coronavirus Disease-2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the need for the development and upgradation of new and existing tools has resurfaced. Latest technological advances in the field of molecular diagnosis have paved the way for providing faster turn-around times for tests, leading to expedited treatment and quarantine decisions. The use of classical and molecular virology tools leads to a better understanding of the virus in the context of the host. The initial diagnosis of the SARS-CoV-2 was carried out by using Next Generation Sequencing (NGS) platforms. Currently, real-time RT-PCR is the gold standard for the laboratory diagnosis of SARS-CoV-2. Serological assays are being used for the detection of antibodies against SARS-CoV-2 for serodiagnosis and to understand the parameters like infection rate and seroprevalence in the community. The present article describes the advancements in the field of viral diagnostics and the role of classical and molecular virology in the context ofthe COVID-19 pandemic response and research.

[*J Indian Med Assoc* 2021; **119(1):** 24-30]

Key words **: Classical virology, Molecular virology, COVID-19, Pandemic, Serology, Epidemiology.**

Viruses make up over two-thirds of all new human pathogens[1]. On an average, more than two new species of human virus are reported every year[2].The current Coronavirus disease (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a public health emergency across the world. During a pandemic situation, diagnostics are fundamental as a primary response for treatment and implementation of prevention and control measures.

The pioneering methods in diagnostic virology were the complement fixation test to detect antibodies and virus isolation using tissue culture during 1929 and 1948 respectively. Eventually rapid diagnosis was possible with the advent of techniques using monoclonal antibodies in the 1970s and molecular methods such as the polymerase chain reaction (PCR) in 1985[3]. The DNA sequencing by chain termination method was first described by Sanger *et al* in the year 1977, and has revolutionized the field of biology[4]. The present article discusses briefly the advancements in the field of viral diagnostics and the role of classical and molecular virology in the context of COVID-19 pandemic response and research.

ICMR-National Institute of Virology, Pune 411021

[1]MSc, PhD, Scientist 'E' and Nodal Officer, Poliovirus Essential Facility and Corresponding Author

[2]MD (PSM), PG Diploma-Bioethics, Scientist 'F' and Group Leader

[3]MSc, ICMR-Senior Research Fellow

[4]MSc, Technical Officer 'B', Poliovirus Essential Facility

[5]MSc, Senior Technical Officer '3', Poliovirus Essential Facility

[6]MD, FRCPath, PhD, Director

Received on : 17/11/2020

Accepted on : 19/11/2020

Editor's Comment :

- **Concerted efforts including classical and molecular virology along with epidemiological studiesin pandemic situation would help in impact assessment, containment and mitigation.**

Role of Classical Virology in COVID-19 :

Since a living system is required to culture viruses, host systems such as cell culture, embryonated chicken eggs and mammalian hosts are used for isolation depending on the preference of the viruses.The influenza virus was first isolated using embryonated chicken eggs in the year 1933[5]. The first two human viruses to be isolated using tissue culture were Mumps and Influenza viruses in 1948[6].

The advantages of virus isolation are that it makes virus available for serological and molecular diagnostic assays, vaccine development, antigenic characterization, studies on morphological and structural aspects, pathogenesis studies and antiviral studies. The only disadvantage of virus isolation is that it is time-consuming,thus cannot be used for diagnostic purposes. SARS-CoV-2 is a culturable virus and has been isolated using Vero CCL-81 and Vero E6 cell lines[7]. It has been shown that SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme

2 (ACE2) for entry and the cellular serine protease TMPRSS2 for S protein priming. Moreover, SARS-CoV-2 shows increased binding affinity to ACE2 as compared to SARS-CoV, thereby making it more pathogenic[8]. India was the fifth country in the world to isolate the virus.

Use of Serological Assays :

Serological assays are required for the detection of specific antibodies against a virus. These include the complement fixation, enzyme-linked immuno-sorbent assay (ELISA), immunofluorescence assay (IFA), hemagglutination inhibition and neutralization assays which could be used for different purposes. The advantages of serological assays are that they could be used to estimate immunity levels and spread of the disease by undertaking large-scale serosurveys. Such studies also enable researchers to determine the stages of infection among the infected individuals, such as acute or convalescent phase. Use of serological assays for vaccine-efficacy studies during clinical trials enables the determination of protective immune response against the vaccine. Immuno-fluorescence assays using virus-infected Vero E6 cells spotted on glass slides and ELISAs using extracts or supernatant of infected cells were among the first assays used in serological diagnosis of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) of 2002[9]. There have been several advancements in the field of diagnosis since the SARS-CoV epidemic. It has been reported that serology testing could be useful to assist sero-diagnosis of SARS-CoV-2[10]. It has also been speculated that in addition to the use of serological data to identify and contain cases, serological studies can also be used to assess how much community transmission has occurred, to determine the immunity of healthcare workers and also to identify individuals who had mounted a strong immune response as possible donors for plasma therapy[11].

The ELISAs, lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays (CLIAs) are the three serological assays which are being widely used for COVID-19 diagnosis. In a meta-analysis carried out for studies reporting serological assays for COVID-19 diagnosis, the pooled sensitivity of ELISAs measuring IgG or IgM was reported as 84.3%, of CLIAs was 97.8% and of LFIAs was 66.0%, which was the lowest[12].The World Health Organization (WHO) also advices cautious use of such rapid immunodiagnostic tests due to the high possibility of false positive results, due to cross-reactivity with other pathogens.

Use of Rapid diagnostic Tests (RDTs) for detection of antibodies and antigensagainst SARS-CoV-2 :

Lateral-flow immunoassays, in the form of Rapid Detection Tests (RDT)are employed for the detection of several diseases and viruses. They facilitate rapid detection of antigens and antibodies. However, they have the limitation of poor sensitivity and specificity. The pooled sensitivity for LFIAs, the potential point-of-care method, was reported lower than that for ELISA and CLIA[12]. The detection of antigens by using RDTs is generally preferred, as the development of antibodies requires time after infection. There are different types of antibodies based on their function like neutralizing, complement fixing, cross-reacting and hemagglutination inhibition antibodies. RDTs are not able to distinguish the exact properties of the antibody. RDTs can also not determine the antibody titres which may be required to study disease progression. The WHO has encouraged research on the performance and potential diagnostic utility of serological rapid detection tests for COVID-19.

In case of respiratory pathogens, the detection of antigens is easier as the virus is shed in the respiratory fluids. The ICMR has issued an advisory on the on the use of an RDT kit called the 'Standard Q COVID-19 Ag detection kit', for the diagnosis of COVID-19[13]. It was reported that the test has a specificity ranging from 99.3 to 100%, and a sensitivity ranging from 50.6% to 84% in two independent evaluations, depending upon the viral load of the patient. Higher viral load correlated with higher sensitivity. The turn-around time for this test was 15 minutes. Though there is no data on the application of this test on a large sample size in clinical setting.

Role of molecular virology in COVID-19 :

The development of PCR techniques has revolutionized the field of diagnostics and research. Multiplex PCR technology has made the diagnosis of multiple pathogens possible at the same time, from a single sample[14]. Molecular assays for the detection of microorganisms can be designed even when only partial nucleic acid sequence information is available. This is valuable for the identification and diagnosis of new diseases and emerging pathogens since the rapid development of in-house assays becomes possible[15]. The advent of real time PCR has enabled detection and absolute quantification of the amplified products in lesser turn-around times, making real time PCR the Gold-standard for molecular diagnosis for viral diseases like influenza H1N1 and more recently, SARS-CoV-2[16]. Although the reverse transcriptase-PCR (RT-PCR) for the diagnosis of COVID-19 is highly specific,

further optimization to mitigate the false negative rate has been recommended on high priority[17]. These assays are also expensive and need to be carried out with utmost precautions, because a lack of PCR discipline causes cross-contamination and can be catastrophic. For COVID-19 testing in India, two more molecular based tests are available apart from RT-PCR, namely, True Nat and CBNAAT (cartridge based nucleic acid amplification test)[18]. The advisory on the testing strategy for COVID-19 has been issued by the ICMR, and has been summarized in Box 1[19].

The latest technology of Next-Generation Sequencing (NGS) enables analysis of the complete genomes of organisms in a relatively shorter time from small quantities of the sample detecting the most subtle differences in the virus genomes. Sequencing and next generation sequencing can reveal the aspects of the origin, pathogenicity markers, antiviral resistance markers, markers for adaptation in humans, etc. The first detection of SARS-CoV-2 was achieved using NGS, which underscored the importance of such platforms for quick diagnosis of unknown etiology[20].The full genome sequencing of the first two SARS-CoV-2 viruses from India was carried out using the Miniseq platform. They were found to represent separate introductions of SARS-CoV-2. In the study, potential T-cell and B-cell epitopes, as potential vaccine targets, were also identified using bioinformatics tools[21]. Modern technologies like ultrastructural analysis, transcriptomic, proteomic, interactome analyses, single cell RNA seq, RNA interference, CRISPR gene editing etc., have revolutionized the field of biology as a whole. Master Regulator Analysis, which elucidated regulatory networks among the SARS-CoV-2 and host cell proteins revealed the parts of the human interactome which are most affected by infection[22]. The immuno-pathological aspects of the disease, as well as the immunological landscape after recovery has been studied in COVID-19 patients using the single-cell RNA sequencing techniques[23]. A promising dual CRISPR-Cas12 a based method for simple, ultrasensitive and visual detection of SARS-CoV-2 and Human Immunodeficiency Virus (HIV) has been developed enabling rapid detection with improved sensitivity of even a few copies of the virus. The development of other tests, like the Reverse transcription loop-mediated isothermal amplification and Recombinase polymerase amplification is also promising but not without certain disadvantages of its own like challenges in primer design, difficulty in quantification, interference from incorrectly folded primers, etc[24]. Such technologies could be used to explore therapeutics and cutting-edge diagnostic tools against this new virus.

Bioinformatics studies based on genome sequencing provide an insight into the structural and evolutionary aspects of the virus. Molecular clocks, phylogeny and phylogeography studies estimate the spatio-temporal features of evolution of the virus. The structural and functional aspects of the virus need to be correlated with laboratory studies. Software for selection pressure analysis, epitope prediction, molecular simulations, molecular docking, etc. can estimate several features of the organism. Structural studies on SARS-CoV-2 have revealed insights into the receptor binding of the virus and also towards vaccine targets[25]. However, these provide only predictions. The exact pathogenesis of a virus in the host system, or the efficacy of vaccines cannot be determined without carrying out experimental studies. This highlights the importance of correlation of such work with virology experiments in the laboratory.

Role of Molecular Epidemiology and Seroepidemiology in Pandemic Response :

Studies on disease surveillance, seroepidemiology, epidemiology, molecular epidemiology and vaccine evaluation in clinical and field use are important during pandemic response and research. The first COVID-19 case detected through the 'Seattle Flu Study', in a specimen collected on February 24, 2020, was the first documented case of community transmission in the United States at the time. These results initiated assessment of the spread of the virus in the Seattle region, which in turn accelerated public health efforts to mitigate the emerging pandemic. Surveillance studies such as multisite monitoring for influenza surveillance could help in early detection of emerging and re-emerging viruses, unusual epidemiological trends and estimation of the disease burden[26]. Networks of Virus Research and Diagnostic Laboratories across countries are important to understand disease dynamics in the community in this regard[27]. Serosurveillance studies during influenza A (H1N1) 2009 pandemic revealed that the virus infection was wide spread in all sections of the community, highlighting the importance of wide spread surveillance to understand disease progression and herd immunity[28]. Vaccine safety, immunogenicity, efficacy and antibody persistence studies on newly developed vaccines help understand the performance of newer vaccines in the community[29]. Retrospective studies with archived specimens during the influenza H1N1 virus pandemic in India revealed a low level of cross-reactive antibodies to the virus in humans in the pre-

pandemic period in Maharashtra, India[30]. Such studies could also be performed for the determination of the seroprevalence status against coronaviruses among the Indian population. Thus, serological assays can answer several questions pertaining to public health as a whole.

For studying the seroprevalence against COVID-19, several studies have been carried out across the world. In a study carried out in Nigeria among healthcare workers, 26% IgG positivity was reported against SARS-CoV-2. This indicates a high exposure rate for the hospital staff and patients[31]. A higher rate of seroprevalence of antibodies against the virus has been reported among healthcare workers as compared to the local community[32]. In another study conducted among healthcare workers in Sweden, apart from a high IgG seroprevalence (19.1%) against the virus, a strong association was noted among study participants with patient contact but without known COVID-19 contact[33]. On the contrary, in another study from Belgium, being involved in clinical care, having worked during the lockdown phase, being involved in care for patients with COVID-19, and exposure to COVID-19–positive co-workers were not associated with seroprevalence, but rather, having a household contact with suspected or confirmed COVID-19 was associated[34].

The field of molecular epidemiology, based on genomic information, has contributed immensely in infectious disease research in the modern times in order to study the origins, evolution and host tropism of viral diseases. It has been established that the SARS-CoV-2 had a bat origin. However, since there is no close association of humans with bat colonies, it has been reported that coronaviruses are transmitted to humans by another animal host. The animal hosts of SARS-CoV and MERS-CoV were found to be civet cats and camels respectively, whereas, for SARS-CoV-2, pangolins are being speculated as the intermediate hosts[35]. It has also been reported that the amino acid sequence in the ACE2 receptor responsible for SARS-CoV-2 binding in farm animals and cats closely resembles the human receptor, which explains the possible ease of the cross of species barrier. Thus, molecular epidemiological studies could be useful in elucidating origin of emerging viruses.

COVID-19: Research Avenues :

One of the most pertinent questions in times of a pandemic caused by a new virus is about the pathogenicity of the virus, and the severity of the disease. Animal studies form an integral part of virology research because experiments using laboratory animals help in building analogies of infections in humans. Such studies help determine the pathogenicity, tissue tropism, virus shedding, modes of transmission and disease symptoms. Pathogenesis studies *in vivo* are essential to understand the potential of the etiological agents to cause severe illness. Several animal models are available for studying pathogenesis and also for pre-clinical trials of candidate vaccines. Rhesus macaques and ferrets are infectable with SARS-CoV-2 and evidence of virus replication and virus shedding in their nasal swabs has been reported[37].

Pandemic situations demand identification of suitable antiviral drugs to mitigate the infection. *In vitro* and *in vivo* studies are used to carry out antiviral assays.The animal model is useful for the correlation of molecular markers conferring antiviral resistance with pathogenicity of the virus. Developing assays for the determination of antiviral efficacy using cell culture or animal models provides clues for the discovery and effects of antiviral drugs. Drug repurposing provides a faster alternative to developing new therapeutics during a pandemic situation. *In silico* studies help in screening the various available antiviral molecules for possible interactions with the target proteins associated either with the virus or the host[38]. The embryonated chicken egg model has also been explored for assessing susceptibility to antivirals[39]. RNA interference based technology has been explored for therapeutic applications for SARS-CoV before, and is being tested for SARS-CoV-2 as well[40].

Zoonotic diseases (also known as zoonoses) are caused by pathogens that are transmitted between animals and humans[41]. The phenomenon of 'reverse zoonosis' has also been reported, where inviruses were found to be the second most common pathogen associated with human-to-animal transmission[42]. Presence of antibodies against pandemic influenza H1N1 2009 virus in pigs underscores importance of animal-human interface studies. It has been shown that 61% of all human pathogens are zoonotic, and have represented 75% of all emerging pathogens during the past decade. This elaborates the need for extensive research on the origin and spread of viral diseases. The SARS-CoV outbreak which occurred in the years 2002-2003 highlighted the fact that infections could be rapidly transmitted across the globe due to globalization and rise in international air travel. The SARS-CoV had spread to nearly 40 countries, causing more than 8000 infections and close to 800 deaths within a span of one year[43].

Till date there have been pandemics caused by influenza viruses, HIV and SARS-CoV-2.Influenza viruses have caused four pandemics in 1918, 1957, 1968 and 2009 by influenza H1N1, H2N2, H1N1 and

pandemic H1N1 2009 viruses, respectively. Six phases of an influenza pandemic have been described based on the circulation of a zoonotic virus among animals followed by its transmission in humans.These phases are - the prevalence of infection among animals (Phase 1), then infection in humans (Phases 2 and 3) leading to human-to-human transmissions locally, followed by eventual spread of the disease in the community and in other geographic regions (Phases 4, 5 and 6)[44].

For the current pandemic of SARS-CoV-2, four stages have been defined for early stage of the disease in people with travel history (Stage 1), local transmission in clusters (Stage 2), community transmission (Stage 3) and stage of uncontrollable spread (Stage 4)[45]. At every phase of a pandemic, laboratory diagnosis is of utmost importance. Table 1

Table 1 — *Applications of Classical and Modern Virology techniques in COVID-19 pandemic response and research*

Assay Types	Technique	Clinical and Diagnostic use	Public health	Basic Research
Molecular assays	NAAT	Nucleic acid detection-qualitative & quantitative	Rapid diagnosis for case confirmation, prevention and control and surveillance	Virology studies
	Sequencing (Sanger and NGS)	Confirmation of sequences, Virus identification	Molecular epidemiology and transmission tracking studies	Genome sequence, Molecular markers, structural bioinformatics, phylogeny, Metagenomic analysis etc.
	Proteomics/ interactomics	Suceptibility / pathogencicity	Contribution in understanding the disease	Host cell regulatory factors, gene expression, identification of drug targets
	Gene manipulation	Intervention following diagnosis	Development of diagnostic tests such as antigen detection tests using recombinant antigens therapeutics such as monoclonal antibodies	Studying pathogenesis, gene splicing, use of recombinant DNA, monoclonal antibodies
Serological assays	ELISA	Antigen/ antibody detection for serodiagnosis	Herd immunity, serosurveillance, seroprevalence, vaccine trials	Host immune response
	RDT/LFIA	Rapid point-of-care serodiagnosis	Screening of susceptibles, studying population level immunity	Serosurveillance
	RDT	Antigen detection	Rapid diagnosis for case confirmation, prevention and control and surveillance	Virology studies
	CLIA	Total antibody detection	Herd immunity, serosurveillance, seroprevalence	Serosurveillance
	IFA	Virus detection in infected cells	Laboratory diagnosis at referral centers, validation of diagnostic assays	Confirmatory for virus isolation, Host-virus interaction studies
	NT	Useful to determine whether antibodies are protective or not	Herd immunity, serosurveillance, vaccine immunogenicity, antibody persistence, efficacy	Protective immune response, Antigen/ epitope identification, Neutralizing antibodies
Virological assays	Virus isolation in cell culture	Confirming diagnosis	Vaccine development	Infectivity, pathogenicity and virulence studies. Basic material used in all branches of research
	Antiviral assays	No	For prophylaxis and treatment	Drug-repurposing,antiviral susceptibility
	Animal experiments	No	Preclinical vaccine trials	Pathogenesis, virus fitness, tissue tropism, monoclonal antibody generation
	Receptor specificity	No	Zoonosis	Pathogenicity, host range

NAAT Nucleic Acid Amplification Tests; ELISA Enzyme Linked Immunosorbent Assay; RDT Rapid Detection Test; CLIA Chemiluminescent Immunoassay; IFA Immunofluorescence Assay; LFIA Lateral Flow Immunoassay; NT Neutralization Test.

ICMR Testing Strategy for COVID-19 testing in India

Setting	Recommended tests (in order of priority)	Whom to test
Containment zones : routine surveillance & screening	1. Rapid Antigen Test 2. RT-PCR or TrueNat or CBNAAT	Symptomatic individuals: healthcare & frontline Asymptomatic individuals: contacts and high-risk
Non-containment zones: routine surveillance	1. RT-PCR or TrueNat or CBNAAT 2. Rapid Antigen Test	Symptomatic individuals: with travel history, direct contacts, healthcare & frontline
	1. Rapid Antigen Test 2. RT-PCR or TrueNat or CBNAAT	Asymptomatic high-risk contacts
Hospitals	1. RT-PCR or TrueNat or CBNAAT 2. Rapid Antigen Test	All symptomatic patients, neonates Asymptomatic patients: high-risk, undergoing invasive procedures, pregnant women
Testing on demand	Whichever applicable	As per request

Advisory for testing strategy is available on the ICMR portal https://www.icmr.gov.in/cteststrat.html

summarizes the various tool that could be or are used for the diagnosis and research of SARS-CoV-2. As the pandemic progresses, diagnosing each and every case without any established predisposition is difficult and unnecessary, since it puts unnecessary pressure on the resources leading to shortage. Eventually, the cases are diagnosed based on clinical symptoms and presumptive treatment and preventive actions are implemented accordingly. However, it will depend on the criticality of diagnosis for treatment and prevention measures. The scientific community across the world is carrying out rigorous research aimed at understanding the virus better, and also towards the development of potential cures and vaccines, which bear utmost importance in this public health emergency (Table 1).

From the Indian perspective, the need has been highlighted to revisit responses to a raging pandemic[46]. The production of local technology-driven solutions including point-of-care diagnostics and research relevant to stages of pandemic should be supported. The scientific community across the world has been working on the development of different technologies like whole virus vaccines, recombinant protein subunit vaccines, and nucleic acid vaccines against SARS-CoV-2[46]. These efforts combined with the pursuit of antiviral drugs provide hope for the control of this pandemic.

The field of virology has evolved tremendously in the 21st Century. Several key developments in the field of biology, like the genesis of molecular virology, gene manipulation, gene transfer, whole genome sequencing, growth of immunology, cell biology and biochemistry have been associated with the discipline of modern virology[47]. While unravelling the mechanisms of replication and pathogenesis of novel viruses, new and interesting aspects of cell biology have also emerged in the recent past. Therefore, the emphasis on classical virology approaches along with the molecular virology in the current pandemic would help in containment, mitigation and understanding of the impact of the pandemic on human health.

Conflicts of interest : None

Author Contributions Statement : Conceptualization of the article: SDP, BVT. Wrote the manuscript: SDP, BVT, DST, SSK, SSK. Reviewed and edited the manuscript: SDP, BVT, DST, SSK, SSK, PA.

Acknowledgements

We would like to thank Dr Jayati Mullick for support and Dr. Sarah Cherian for critical review of this article. The Indian Council of Medical Research is also acknowledged.

References

1 Woolhouse M, Gaunt E — Ecological origins of novel human pathogens. *Crit Rev Microbiol* 2007; **33:** 231-42. https://doi.org/10.1080/10408410701647560
2 Woolhouse ME, Howey R, Gaunt E, *et al* — Temporal trends in the discovery of human viruses. *Proc R Soc B* 2007; **275:** 2111-5. https://doi.org/10.1093/biohorizons/hzw010
3 Storch GA — Diagnostic Virology. In: Knipe DM, Howley PM (eds) Fields Virology, 5th Edition. Lippincot Williams & Wilkins 1996; pp 566–604.
4 Sanger FSN, Coulson A — DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci, USA* 2007; **74:** 5463-7. https://doi.org/10.1097/00006250-199004001-00013
5 Smith W, Andrewes CH, Laidlaw PP — A Virus Obtained from Influenza Patients. *Lancet* 1933; 66-8.
6 Weller TH, Enders JF — Production of Henlagglutinin by Mumps and Influenza A Viruses in Suspended Cell Tissue Cultures. *Proc Soc Exp Biol Med* 1948; **69:** 124-8.
7 Harcourt J, Tamin A, Lu X, *et al* — Severe Acute Respiratory Syndrome Coronavirus 2 from Patient with 2019 Novel Coronavirus Disease, United States. *Emerg Infect Dis* 2020; **26:** https://doi.org/10.3201/eid2606.200516
8 Hoffmann M, Kleine-Weber H, Schroeder S, *et al* — SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181: 271-80. e8. https://doi.org/https://doi.org/10.1016/j.cell.2020.02.052
9 Infantino M, Damiani A, Gobbi FL, *et al* — Serological assays

for SARS-CoV-2 infectious disease: Benefits, limitations and perspectives. *Isr Med Assoc J* 2020; **22:** 203-10.
10 Xu Y, Xiao M, Liu X, *et al* — Significance of Serology Testing to Assist Timely Diagnosis of SARS-CoV-2 infections: Implication from a Family Cluster. *Emerg Microbes Infect* 2020; **0:** 1-12. https://doi.org/10.1080/22221751.2020.1752610.
11 Winter AK, Hegde ST — The important role of serology for COVID-19 control. *Lancet Infect Dis* 2020; S1473-3099:30273–4. https://doi.org/10.1016/S1473-3099(20)30322-4.
12 Lisboa Bastos M, Tavaziva G, Abidi SK, *et al* — Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. *BMJ*; **370:** m2516. https://doi.org/10.1136/bmj.m2516.
13 Indian Council of Medical Research (2020) — Advisory on Use of Rapid Antigen Detection Test for COVID-19. https://www.icmr.gov.in/pdf/covid/strategy/Advisory_for_rapid_antigen_test14062020.pdf. Accessed 13 Jul 2020.
14 Storch GA — Diagnostic Virology. In: Reller LB, Weinstein MP (eds) Clinical Infectious Diseases, Special section: Medical microbiology 2000; pp 739-51.
15 Read SJ, Burnett D, Fink CG — Molecular techniques for clinical diagnostic virology. *J Clin Pathol* 2000; **53:** 502-6. https://doi.org/10.5505/TurkHijyen.2015.99705
16 Kiselev D, Matsvay A, Abramov I, *et al* — Current Trends in Diagnostics of Viral Infections of Unknown Etiology 2020; **12:** 211. https://doi.org/10.1111/j.1365-2559.2008.02964.x. Involvement
17 Touma M — COVID-19: molecular diagnostics overview. *J Mol Med* 2020; **98:** 947-54. https://doi.org/10.1007/s00109-020-01931-w
18 Indian Council of Medical Research Strategy for COVID-19 testing in India. https://www.icmr.gov.in/pdf/covid/strategy/Testing_Strategy_v6_04092020.pdf
19 Indian Council of Medical Research (2020) — Information on testing strategies. https://www.icmr.gov.in/cteststrat.html
20 Tan W, Zhao X, Ma X, *et al* — Notes from the Field: A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases — Wuhan , China 2019 " 2020. *China CDC Wkly* 2020; **2:** 61-2.
21 Yadav PD, Potdar VA, Choudhary ML, *et al* — Full-genome sequences of the first two SARS-CoV-2 viruses from India. *Indian Jounral Med Res* 2012; **151:** 200-9. https://doi.org/10.4103/ijmr.IJMR.
22 Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM — Master Regulator Analysis of the SARS-CoV-2/Human Interactome. *J Clin Med* 2020; **9:** 982. https://doi.org/10.3390/jcm9040982
23 Liao M, Liu Y, Yuan J, *et al* — Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med 2019; https://doi.org/10.1038/s41591-020-0901-9.
24 Molecular-based Tests for COVID-19. https://www.centerforhealthsecurity.org/resources/COVID-19/molecular-based-tests/. Accessed 13 Jul 2020.
25 Robson B — Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus. *Comput Biol Med* 2020; **119:** 103670. https://doi.org/10.1016/j.compbiomed.2020.103670.
26 Chadha MS, Broor S, Gunasekaran P, et al — Multisite virological influenza surveillance in India: 2004-2008. *Influenza Other Respi Viruses* 2012; **6:** 196-203. https://doi.org/10.1111/j.1750-2659.2011.00293.x
27 Gupta N, Potdar V, Praharaj I, *et al* — Laboratory preparedness for SARS-CoV-2 testing in India: Harnessing a network of Virus Research & Diagnostic Laboratories. *Indian Jounral Med Res* 2020; **594:** https://doi.org/10.4103/ijmr.IJMR.
28 Tandale B V, Pawar SD, Gurav YK, *et al* — Seroepidemiology of pandemic influenza A (H1N1) 2009 virus infections in Pune, India. *BMC Infect Dis* 2010; **10:** 255. https://doi.org/10.29333/ejgm/82752.
29 Tandale BV, Pawar SD, Mishra AC — Immunogenicity and safety of pandemic H1N1 2009 vaccine among adults in field use, India. *Vaccine* 2012; **30:** 2043-44. https://doi.org/10.1016/j.vaccine.2011.10.008.
30 Kode SS, Pawar SD, Tandale BV, *et al* — Low level of cross-reactive antibodies to pandemic influenza (H1N1) 2009 virus in humans in pre-pandemic period in Maharashtra, India. *Indian J Virol* 2012; **23:** 36-8. https://doi.org/10.1007/s13337-011-0055-y.
31 Asuquo MI, Effa E, Otu A, *et al* — Prevalence of IgG and IgM antibodies to SARS-CoV-2 among clinic staff and patients. *Med Rxiv* 2020; 2020.07.02.20145441. https://doi.org/10.1101/2020.07.02.20145441.
32 Schmidt SB, Grüter L, Boltzmann M, Rollnik JD — Prevalence of serum IgG antibodies against SARS-CoV-2 among clinic staff. *PLoS One* 2020; **15:** e0235417.
33 Rudberg A-S, Havervall S, Manberg A, *et al* — SARS-CoV-2 exposure, symptoms and seroprevalence in health care workers. *med Rxiv* 2020; 2020.06.22.20137646. https://doi.org/10.1101/2020.06.22.20137646
34 Steensels D, Oris E, Coninx L, *et al* — Hospital-Wide SARS-CoV-2 Antibody Screening in 3056 Staff in a Tertiary Center in Belgium. *JAMA* 2020; https://doi.org/10.1001/jama.2020.11160
35 Jin Y, Yang H, Ji W, *et al* — Virology, epidemiology, pathogenesis, and control of covid-19. *Viruses* 2020; **12:** 1-17. https://doi.org/10.3390/v12040372
36 Sun J, He W-T, Wang L, *et al* — COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. *Trends Mol Med* 2020; **26:** 483-95. https://doi.org/https://doi.org/10.1016/j.molmed.2020.02.008
37 WHO R&D Blueprint, COVID-19 Animal Models. https://www.who.int/blueprint/priority-diseases/key-action/WHO-ad-hoc-Animal-Model-Working-Group_Summary.pdf?ua=1. Accessed 2 May 2020
38 Cherian SS, Agrawal M, Basu A, *et al* — Perspectives for repurposing drugs for the coronavirus disease 2019. *Indian Jounral Med Res* 2020; 160-71. https://doi.org/10.4103/ijmr.IJMR
39 Tare DS, Pawar SD — Use of embryonated chicken egg as a model to study the susceptibility of avian influenza H9N2 viruses to oseltamivir carboxylate. *J Virol Methods* 2015; **224:** https://doi.org/10.1016/j.jviromet.2015.08.009.
40 Wu C, Chan Y — Antiviral applications of RNAi for coronavirus. 2006; 89-97.
41 Zoonotic Diseases | One Health | CDC. https://www.cdc.gov/onehealth/basics/zoonotic-diseases.html. Accessed 2 May 2020
42 Messenger AM, Barnes AN, Gray GC — Reverse zoonotic disease transmission (Zooanthroponosis): A systematic review of seldom-documented human biological threats to animals. *PLoS One* 2014; **9:** 1-9. https://doi.org/10.1371/journal.pone.0089055
43 Marston HD, Folkers GK, Morens DM, Fauci AS — Emerging viral diseases: Confronting threats with new technologies. *Sci Transl Med* 2014; **6:** 1-7. https://doi.org/10.1126/scitranslmed.3009872
44 WHO pandemic phase descriptions and main actions. https://www.who.int/influenza/resources/documents/pandemic_phase_descriptions_and_actions.pdf. Accessed 2 May 2020
45 (2020) Coronavirus: The four stages of a global pandemic | The Economic Times. Econ. times
46 Chen WH, Strych U, Hotez PJ, Bottazzi ME — The SARS-CoV-2 Vaccine Pipeline: an Overview. *Curr Trop Med Reports* 2020; 1-4. https://doi.org/10.1007/s40475-020-00201-6
47 DiMaio D — Is Virology Dead? 2014; MBio 5:. https://doi.org/10.1128/mBio.01003-14.

Review Article

New Strain SARS CoV2

Partha S Ray[1]

Under severe strain for nine months of 2020, with 1.8 million deaths through Covid 19 and 85 million people infected, we were all hoping 2021 would show us the light at the end of the tunnel. The "new variant" of SARS-CoV-2 and its confirmed rapid transmission properties has once more setback our hopes. The start of vaccinations in the last week has been a source of relief although the benefits of the same will only be known with the passage of time. New variants and mutations against which the vaccines have not been prepared will continue to be challenges on a daily basis for scientists epidemiologists and administrators. Despite treating Covid 19 patients of all spectrums with a variety of therapeutic agents only a few like oxygen and steroids have acquired some evidence basis while others have not met the same threshold. The public have suffered including through anxiety and education, livelihood and social structure have suffered to the point of breaking in these tumultuous times. Patience is a virtue and prevention measures– hand hygiene wearing of masks social distancing and avoiding unnecessary human contact will eventually see us through with vaccines being the added layer of protection and prevention.

[*J Indian Med Assoc* 2021; **119(1):** 31-6]

Key words **: "new variant" of SARS-CoV-2, Vaccinations, Covid 19, Self Isolation, Masks.**

SARS-CoV-2 has infected more than 85 million persons and caused more than 1.85 million deaths approximately till early January 2021. Hopes have risen with the commencement of vaccination against the virus which have commenced in the UK initially and next in the US with other countries including India to follow shortly. However new strains including the recently identified "variant of concern (VOC)" in UK which clearly has a higher transmissibility has raised concerns from a public health standpoint.

The genetics of this novel RNA virus merits closer attention by the medical community at large so that we all have a clear understanding of the RNA virus pathogenesis, virulence, transmissibility and now the level of protection achieved through vaccination programs[1]. Mutations in RNA viruses are inevitable as they replicate and circulate. Most mutations are of no consequence while others may be neutral or of a positive survival advantage to the virus. Many thousands of mutations have been identified in the SARS-CoV-2genome. Novel combinations of mutations are appearing. While the most mutations had no apparent effect on the virus,a minority can change the virus by increasing its infectivity or cause a change in the clinical severity or in the way the virus interacts with the immune system including the vaccine response. Most attention has been paid to mutations in the genes that encode the spike protein and therefore determine immunity and vaccine efficacy.

Editor's Comment :

- **Preventative measures are paramount and the basic principles of hand hygiene, wearing of masks, staying apart physically and avoiding unnecessary travel and social congregation unless legally authorised and seeking medical help and self isolating at the earliest warning signs of Covid 19 infection remain the cornerstones of our fight against the coronavirus.**
- **Vaccination will certainly help against strains that are sensitive to it and it is hoped the new mutants and variants will also be protected against.**
- **The World Health Organisation and our respective national governments efforts, people's togetherness and the strength of the global human race will surely manage to beat back the ravages caused by this tiny RNA virus.**

History of SARS-CoV-2 genomics: the virus probably originated in bats and strains found in Wuhan, China showed very less genetic diversity meaning that the virus may have been introduced from a single source[2]. Early zoonotic variants in the novel coronavirusSARS-CoV that emerged in 2003 targeted the receptor binding domain (RBD) of the spike protein and thereby increased entry through the human angiotensin-converting enzyme 2 (hACE2) receptor[3]. The spike protein RBD of earlySARS-CoV-2 strains were shown to affect the hACE2 receptors early on[2].

In the UK, the COVID-19 genomics UK

[1]MBBS, DTM&H, MD (Medicine), DNB (Medicine) MRCP (UK-Neurology), FRCP (London and Edinburgh), DNB (Neurology), CCST (Neurology & Clinical Neurophysiology), Consultant Neurologist and Neurophysiologist, NHS England and Clinical Lecturer Liverpool University and Post Graduate Medical School Liverpool & Hony IMA National Professor in Neurology

Received on : 06/01/2021
Accepted on : 10/01/2021

consortium(COG-UK) has been maintaining a close watch on the evolving genetics of SARS-CoV-2 since the onset of infections. COG-UK undertakes sequencing of SARS-CoV-2 samples from about 10% of confirmed cases in the UK. Public Health England and New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) work in close association with COG – UK to be able to adviseScientific Advisory Group for Emergencies (SAGE) of the best advice the British government can give to UK citizens and advice the global community via the World Health Organisation to provide advance genomic information on this pandemic virus to prevent its further spread.

Historically in late February 2020 D614G mutation affecting the spike glycoprotein SARS-CoV-2 from southern Europe was found, and this variant has since has become the most common genotype worldwide[4]. This variant had higher viral loads in the upper respiratory tract than poeple with the virus strains without the mutation although the disease severity was not affected[5].

On 8 December 2020, an increasing incidence of COVID 19 cases was detected in Kent, England as part of epidemiological surveillance of the genomic data that revealed the Kent cluster[6]. This cluster was phylogenetically very distinct from the rest of the UK data set. These cases were concentrated in Kent and north-east London with limited spread into rest of London, Anglia and Essex. This variant(familiar now as the "new variant") was designated as a variant under investigation (VUI) redesignated as VOC –202012/01 on 18 December 2020[7]. The lineage of this new SARS-Cov-2 was termed B.1.1.7 which was first observed in the UK in September 2020 and had spread to at least 244 of 317 English local authorities by December 13, 2020[8]. Initially high prevalence was seen in the south-east of England and was contributing to an increasing share of cases locally and nationally. High transmissibility relative to other circulating lineages (estimated to be 1.5 to 1.7-fold higher) despite the English lockdown between November 5 and December 2, 2020 during which case numbers was generally contracting was noted[9].

The particular feature of this "new variant" of SARS-CoV-2 genomics[10] was the appearance of 23 mutations: 13 non-synonymous mutations, four deletions and six synonymous mutations[11]. Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineageare enumerated in table 1and others in the open reading frame and one in the M gene. This was the appearance of an unusually large number of mutations in a single cluster so far (Table 1a. Priority mutations tracked by COG-UK,Table 1b. Priority lineages tracked by COG-UK)Most mutations are not concerning because they do not result in a change in one of the nucleotides that generate the proteins the virus is made of. When they do that becomes serious specially when the mutations occur in a region of the virus that could change the way it interacts with its human host. In this case changes in the spike protein which projects outside the virus and is the mechanism by which it attaches to enter the host cell where it can replicate becomes of great interest. The lineage B 1.1.7 has one mutation termedN501Y [12](denotes the wildtype N Asparagine replacement with amino acid Y Tyrosine)that had been shown to increase how tightly the protein combines to a receptor on the surface of the human cell. A second change (69 – 70 deletion) had been identified in viruses that evolved to evade the natural immune response in some immune compromised patients. How this large cluster of mutations occurred simultaneously is a conjecture including viral replication under selective pressures in an alternative host (for example the Danish cluster in minks) or possibly in an immune compromised patientwho was chronically infected with the virus and able to replicate and evolve in them over a long period of time. These hypotheses remain unproven.

Potential impact of spike variant N501Y[13] :

(a) Transmissibility: the new variant has increased transmissibility characterised by an absolute increase in the R value of between 0.39 -0.93. This is likely through the N501Y affecting the receptor binding affinity of the spike protein is enhancing the transmissibility of the virus.

(b) Antigenicity: position 501 is in the receptor binding domain where neutralising antibodies most frequently act and therefore it is possible that variants at this position affect the efficacy of neutralisation of the virus.

(c) The growth rate from genomic data suggests that it is 71% higher than other variants.

(d) The PCR ct values suggest a decrease of cyclical time value of around two with the new variant

(e) the emergence and subsequent dominance of the new variant does suggest that the new variant has a selective advantage over other variants.

(f) The stability and growth potential of the new strain during a period when National lockdown measures were taken suggests a higher replicative potential of the new strain.

As of the 18 December 2020 NERVTAG[14]opined that there was currently insufficient data to draw any conclusions on:

Table 1 — *Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineage.(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Gene	Nucleotide	Amino acid
ORF1ab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 deletion
Spike	21765-21770 deletion	HV 69-70 deletion
	21991-21993 deletion	Y144 deletion
	A23063T	N501Y
	C23271A	A570D
	C23604A	P681H
	C23709T	T716I
	T24506G	S982A
	G24914C	D1118H
Orf8	C27972T	Q27stop
	G28048T	R52I
	A28111G	Y73C
N	28280 GAT->CTA	D3L
	C28977T	S235F

(1) underlying mechanisms of increased transmissibility

(2) the age distribution of cases

(3) disease severity (4 deaths from around 1000 cases till 18/12/2020)

(4) antigenic escape: the location of the mutations in the receptor binding domain of the spike glycoprotein which raises the possibility that this variant is antigenically distinct from prior variants. Four probable reinfections have been identified among 915 subjects with this variant and further work was needed to compare this reinfection rate with compatible data sets.

(5) Within the UK the variant was concentrated in the London, south-east and East of England but had been detected in various parts of the UK as part of its spread.

(6) Few cases of this variant have been reported internationally including export from the UK to Australia and to India. (As of 30 December, VOC-202012/01 variant has been reported in 31 other countries/territories/areas in five of the six WHO regions.)[13]The UK sequencing capabilityis acknowledged to be very robust for new genotypes as well as for epidemiological surveillance.

(7) NERVTAG endorsed the actions proposed by Public Health England and suggested better comparative data on reinfection, readmission and case fatality rates acquisitions, better data on age distribution of infections and in vitrio data on the ability of convalescent and post-immunisation sera to neutralise the new variant.

Effect of Vaccinations :

With vaccinations being rolled out in the UK there is no evidence so far to suggest that the current vaccination targets are not effective against the new variant. However, this is subject to confirmation and in the absence of genotype testing prior to mass vaccination the Chief medical Officer Sir Chris Whitty[15] has advised routine vaccination. The Prime Minister Mr Boris Johnson on 19 December 2020 also endorsed the same view where he reported absence of evidence to suggest the vaccine will be any less effective against the new variant. In the light of this resurgence of "new variant" SARS-CoV-2 infections fresh lockdown and tiered containment strategies are again in force throughout the UK. The PM Mr Johnson reluctantly to save lives announced a third lockdown on and from 5

Table 1a — *Priority mutations being tracked by COG-UK(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Mutation	Predominant Lineage	Reasons for tracking	Cumulative number in UK	Number over last 28 days (13/11/2020 - 10/12/2020)
D614G	B.1	Moderate effect on transmissibility	118,906	11,447
A222V	B1.177	Fast growing lineage but no evidence of mutation effect	46,710	7,856
N439K	B.1.141 B.1.258	(1) Increased binding affinity to hACE2receptor	3,320	246
		(2) Escape to somemAbs	3,504	1,228
Δ69-70	B.1.1 B.1.258	Possible escape to some mAbs		
N501Y	B.1.1.7	Fast growing lineage & increased binding affinity to hACE2 receptor	2,057	1,182
N501Y+Δ69-70	B.1.1.7	Likely to maintain characteristics described for N501Y and 69-70del	1,524	1,034
N439K+Δ69-70	B.1.258	Likely to maintain characteristics described for N439Y and 69-70del	1,895	176
Y453F	B.1.1 B.1.1.298	(1) Increase binding affinity to hACE2receptor		
		(2) Escape to somem Abs Human/ minkassociated	0	0

Cumulative number as of December 15 based on data deposited into CLIMB. Caution is required since the data will not include information from the last 2 weeks.

Jan 2021[16] to enable the vaccine to take effect and in the meantime to avoid loss of lives and overwhelming the health services that are on the brink and particularly the ITU's and Ventilatory care services. The country since the onset of the pandemic has been divided into four tier zones and presently about 80% of the country is in the higher tiers with the South of England predominantly in Tier 4 with severe restrictions to avoid viral transmission. As a consequence, all social mixing has been curtailed both indoors and outdoors with contacts limited to close family only and a total ban on congregations at public places. Advice on hand hygiene, the wearing of masks, social distancing and avoiding congregation is what one is regularly reminded of on the media waves. Schools remain closed and working from home unless otherwise mandatory remains the ongoing order for the last nine months. Experience from brief relaxations of the above restrictions have only demonstrated how intensively transmissible this virus and its variants are the moment we let our guard down. This precaution against spread and ultra-vigilance has become the order of the day.

Will the vaccine still work?[17] The new variant has mutations to the spike protein that the three leading vaccines are

Appendix (Ref: ICOG – UK - COVID 19 genomics UK Consortium)

The extent to which SARS-CoV-2 may evolve to escape immunity induced by infection or vaccination is not currently known. Determining phenotype from genetic data is a fundamental challenge. **Figure 1a** shows the localisation of the selected mutations in a three dimensional structure of the Spike protein. A222V and the 69-70 deletion are localised relatively far from the receptor-binding site in comparison with amino acid residues 453, 439 and 501 which are in the RBD region. For each amino acid present in the Spike structure, an antibody accessibility score was calculated in **Figure 1b**. High antibody accessibility scores for 501, 439 and 70 correspond to sites that sit on the surface of the protein and that are more easily accessible to antibodies. Antibodies (Ab) are known to recognise specific regions of the Spike protein known as epitopes. Depending on the areas that Abs target there are 4 classes for the RBD region and 1 class for the N-terminal domain (NTD) near to where 69-70 sit (**Figure 1c-d**).

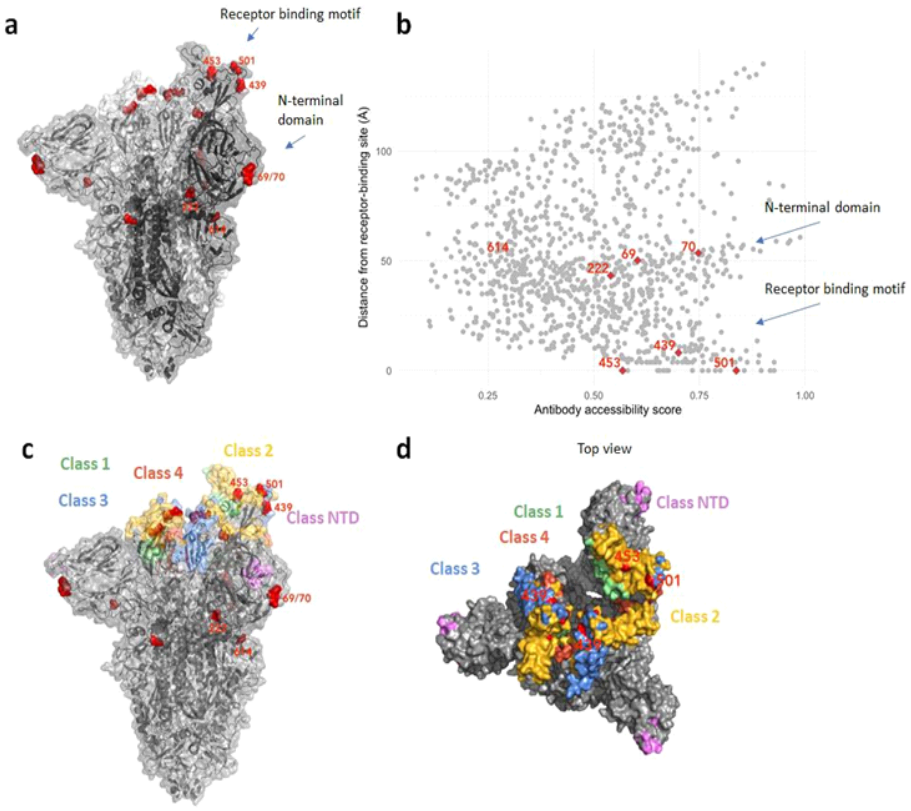


Fig 1 — Localisation of mutations in the Spike structure. a) Spike heterotrimer in open conformation (PDB: 6ZGG, Wrobel et al. 2020). Locations of deleted residues His69 and Val70 and the residues involved in substitutions (A222V, N439K, Y453F, and N501Y) are highlighted in red; b) Each point represents a Spike protein amino acid residue positioned according to distance from the hACE2 receptor-binding site and an antibody accessibility score. Residues associated with high interest amino acid substitution or deletions are highlighted with red diamonds. Residues belonging to the receptor-binding site defined as those with atoms within 4Å in Spike:hACE2 complex and distance to these residues based on closed conformation Spike. Antibody accessibility score represents surface accessibility and amino acid identity of target residue and weighted average of nearby residues and is scaled between minimum 0 and maximum 1, calculated across Spike in open and closed conformations; residues are positioned according to their maximum score across Spike in either open and closed conformations; c-d) Highlighted in colours regions target by different classes of Abs. 453, 501 and 439 are localised in the regions targeted by some classes of mAbs. 69-70 is near a region targeted by other mAbs and deletion might alter the structure of neighbouring amino acids. green = class 1: ACE2 blocking, bind open RBD only; yellow = class 2: ACE2 blocking, bind open and closed RBD; blue = class 3: non-ACE2 blocking, bind open and closed RBD; orange = class 4: non_ACE2 blocking, bind open RBD only). Epitope residues described in the NTD are coloured in magenta.

targeting. However, vaccines produce antibodies against many areas in the spike protein, so a single change would not make the vaccine less effective.

Over time, with more mutations , the vaccine may need to be changed. This happens with seasonal flu, which mutates every year, and the vaccine is altered accordingly. The SARS-CoV-2 virus does not mutate as often as the flu virus, and the vaccines that have so far proved effective in trials are types that can easily be modified if necessary. In India, several vaccines are being rolled out with different targets and different schedules. It is hoped that the mutations do not affect the efficacy of the vaccine and the vaccine effect is lasting – these are matters that are yet to be accurately fathomed.

Herd immunity[18] : at the onset of the pandemic in UK, the public health strategy was to build up herd immunity. However, when the virulence of the virus andunpredictability in its clinical manifestations in various age groups became apparent and the healthcare resources were getting overwhelmed including infections among medical personnel, the above lockdown/containment initiatives were initiated to avoid the number of deaths and to avoid overwhelming the health services. However new variants like this one and the other virus mutations that are being regularly monitored and tracked by COG-UK have regularly nearly pushed health resources to the brink.

As scientists and epidemiologists work overtime to determine the genetic changes theSARS-CoV-2 acquires and vaccines that have been produced in a fast tracked manner are rolled out to develop population immunity against the specified vaccine viral components, it is hoped the population will acquire the basic immunity againstSARS-CoV-2 and its various variants, mutations and lineages to build up herd immunity to stop its spread among nations despite strict travel restrictions and domestic population containment strategies that have been in force for several months now. As vaccines are given it will be important to sequence SARS-CoV-2 virus from infected people who have been vaccinated or had a second infection with the aim to detect variants that are evading the immune system produced by past infection or vaccination. The extent to whichSARS-CoV-2 may evolve to escape immunity induced by infection or vaccination is not currently known. Determining phenotype from genetic data is challenging. – localisation of mutations in the spike structure – appendix 2.

Epidemiological studies have confirmed that new infection rates decline with strict infection-control measures unless "new variants" with higher transmissibility and infectivity and new relations with the host immunity set the clock back and generate clinical cases to the detriment of people's lives and healthcare resource. This seesaw battle with the virus has been the feature of our struggle for nearly all of 2020 as people, businesses and social activities continued to suffer globally.

Priority mutations being tracked by COG-UK[19]: in addition to the "new variant" arising from mutation N501Y and deletions 69 – 70 of the predominant lineage B.1.1.7 a few other mutations and the "cluster five variant" (Danish mink variant) are also being tracked on a matter of priority from the public health point of health protection strategy. A major impediment is our lack of understanding of the various mutations including

Table 1b — *Priority lineages being tracked by COG-UK(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Variant	*Reason for tracking*	*Cumulative number in the UK*	*Number overlast 28 days (13/11/2020 - 10/12/2020)*
'Cluster 5 variant'	Danish Mink variant. Contains 4 mutations including: Y453F, 69-70del, I692V and M1229I. Cluster 5 variants may be able to escape the effect of convalescent plasma. Y453F has increased binding affinity to the human ACE2 receptor in laboratory experiments	0	0
B.1.1.7 (variant)[1]	Has 17 mutations (14 replacements and 3 deletions) including: T1001I, A1708D, I2230T, SGF 3675-3677 del In the ORF1ab; 69-70 del, Y144 del, N501Y, A570D, P681H, T716I,S982Aand D1118H in the Spike; Q27stop, R52I and Y73C in ORF8; D3L and S235F in the N. Noteworthy N501Y enhances ACE2 binding affinity, 69-70del has immunological role and it is associated with some diagnostics failures,and P681H occurs at the furin cleavage site, known for biological significance in membranefusion	1416	945

[1]Named by Public Health England as VUI-202012/01 (the first "Variant Under Investigation" in December 2020)

of potentially structurally important areas of the spike protein and the interactions of the virus with the host.

Way forward as of 5 Jan 2021 in the UK[20]: The PM Mr Boris Johnson announced a third national lockdown last night at 8 pm to save lives and avoid the National Health Service getting overwhelmed. It is hoped that the massive rollout of the vaccination programme with build-up of population immunity in the next 2-3 weeks to prevent spread of the virus and clinical illness. In the meantime, we must all wear face masks, wash our hands for 20 secs and or use hand gel, have 2 m social distancing, avoid all unnecessary travel and congregation and listen to administration guidelines to save and protect lives. In India it is hoped the new variant is contained pre-emptively as it spreads very fast and its clinical manifestations and response to current vaccination targets are yet not certain. With the new variant already spread to 31 countries we can only rely on extreme vigilance and caution to save ourselves and all around us and cooperate with administration at all times.

References

1 Lam TT, Zhu H, Guan Y, Holmes EC — Genomic Analysis of the Emergence, Evolution, and Spread of Human Respiratory RNA Viruses. *Annu Rev Genomics Hum Genet* 2016 Aug 31; 17: 193-218. doi: 10.1146/annurev-genom-083115-022628. Epub 2016 May 23. PMID: 27216777.

2 Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F — Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020 May;581(7807):221-224. doi: 10.1038/s41586-020-2179-y. *Epub* 2020 Mar 30. PMID: 32225175; PMCID: PMC7328981.

3 Chinese SARS Molecular Epidemiology Consortium — Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. Science. 2004 Mar 12;303(5664):1666-9. doi: 10.1126/science.1092002. Epub 2004 Jan 29. PMID: 14752165.

4 Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, *et al* — Sheffield COVID-19 Genomics Group, McDanal C, Perez LG, Tang H, Moon-Walker A, Whelan SP, LaBranche CC, Saphire EO, Montefiori DC. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020 Aug 20;182(4):812-827.e19. doi: 10.1016/j.cell.2020.06.043. Epub 2020 Jul 3. PMID: 32697968; PMCID: PMC7332439.

5 Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, *et al* — Spike mutation D614G alters SARS-CoV-2 fitness. Nature. 2020 Oct 26. doi: 10.1038/s41586-020-2895-3. Epub ahead of print. PMID: 33106671.

6 Lineage-specific growth of SARS-CoV-2 B.1.1.7 during the English national lockdownPreliminary report.Harald Vöhringer1, Matthew Sinnott2, Roberto Amato2, Inigo Martincorena2, Dominic Kwiatkowski2, Jeffrey C. Barrett2 and Moritz Gerstung1, on behalf of The COVID-19 Genomics UK (COG-UK) consortium - 1 European Molecular Biology Laboratory, European Bioinformatics Institute EMBL-EBI, 2 Wellcome Sanger Institute, 3 https://www.cogconsortium.uk 44

7 Public Health England, Investigation of novel SARS-COV-2 variant Variant of Concern 202012/01https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/947048/Technical_Briefing_VOC_SH_NJL2_SH2.pdf 10

8 Minutes of NERVTAG meeting on SARS-CoV-2 variant under investigation VUI-202012/01. URL https://app.box.com/s/3lkcbxepqixkg4mv640dpvvg978ixjtf/file/756963730457 5

9 Nicholas Davies et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. URL https://cmmid.github.io/topics/covid19/uk-novel-variant.html

10 Ceraolo C, Giorgi FM — Genomic variance of the 2019-nCoV coronavirus. J Med Virol. 2020 May;92(5):522-528. doi: 10.1002/jmv.25700. *Epub* 2020 Feb 19. PMID: 32027036; PMCID: PMC7166773.

11 Covid-19: New coronavirus variant is identified in UKBMJ 2020; 371 doi: https://doi.org/10.1136/bmj.m4857 (Published 16 December 2020)Cite this as: BMJ 2020;371:m4857

12 Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, *et al* — Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science. 2020 Sep 25;369(6511):1603-1607. doi: 10.1126/science.abc4730. Epub 2020 Jul 30. PMID: 32732280; PMCID: PMC7574913.

13 SARS-CoV-2 VariantsDisease Outbreak News31 December 2020https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

14 The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advises the government on the threat posed by new and emerging respiratory viruses.https://www.gov.uk/government/groups/new-and-emerging-respiratory-virus-threats-advisory-group

15 Statement from Chief Medical Officer, Professor Chris Whitty, about new strain of COVID-19New strain of COVID-19 reported to World Health Organization.https://www.gov.uk/government/news/statement-from-chief-medical-officer-professor-chris-whitty-about-new-strain-of-covid-19

16 Boris JohnsonPosted at 20:3120:31PM: 'We need to do more to control new variant'https://www.bbc.co.uk/news/topics/c8nq32jw8r1t/boris-johnson

17 Johns Hopkins MedicineCOVID-19 Vaccine: What You Need to Knowhttps://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/covid-19-vaccine-what-you-need-to-know

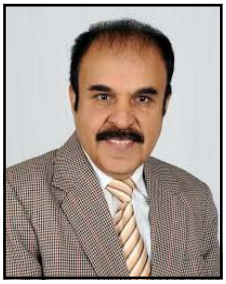
18 Johns Hopkins Bloomberg School of Public Healthhttps://www.jhsph.edu/covid-19/articles/achieving-herd-immunity-with-covid19.html

19 COVID-19 Genomics UK Consortium https://www.cogconsortium.uk/data/

20 Coronavirus (COVID 19)National lockdown: stay at homeYou must stay at home. This is the single most important action we can all take to protect the NHS and save lives.You must not leave your home unless necessary. Stay 2 metres apart from anyone not in your household or bubble.https://www.gov.uk/coronavirus

Voice of the Expert

Adult Vaccination : Some Frequently asked Questions & Answers



Dr A Muruganathan
MD, FICP, FRCP (Glasg & London), FRCP Ireland (Hon), FACP (USA), FPCP (Philippines), Tirupur, Tamilnadu

Question : Why is HPV vaccine approved from 9 to 45 years in India whereas in many countries like USA it is approved from 9 to 26 years?

Answer — In many countries QHPV is approved from 9 to 26 years. In many countries the approval is sought up to 45 years based on the efficacy trials named FUTURE 3 trials in which efficacy for the age group 24 to 45 was shown to be around 90% (89% to be precise). Thus, based on the results of FUTURE 3 studies the ADULT WOMAN INDICATION (AWI) was granted. Currently QHPV is approved in 135 countries and in 54 countries for the age group of 9 to 45 i.e. AWI. India, Canada, Australia, New Zealand are examples of some countries where it is approved from 9 to 45 yrs.

In countries like USA, vaccines are given through either public or private insurer, which compels them to give it in best recommended age i.e. primary schedule and in catch up vaccination schedule for those missed during primary vaccination age. Also cost effectiveness would be more if it is given in age when you would get better immune response and ultimately clinical benefits.

Question : What is the maximum duration of protection that can be given with QHPV. Our patients ask us "will I be protected against cervical cancer forever"

Answer — QHPV was developed and launched in the year 2006. Mathematical models have predicted that protection (antibody titers) will last up to 32 years upon completion of 3rd dose.

In addition, many subjects from NORDIC countries (Denmark, Norway, Iceland & Sweden) are being followed up from 2003 till now. This data is called as NORDIC data or LTFU (Long term Follow up) data. The 14-year findings of this NORDIC data was presented at EUROGIN in 2018 and NO BREAKTHROUGH CASE was found. As of June 2020 the NORDIC data is published.

- Long term data from age of 9 to 26 yrs (NORDIC data) – 14 years no breakthrough (100% effectiveness)
- Long term data from age of 24 to 45 yrs – 10 years no breakthrough.

Question : I know there are 3 doses but what happens if someone misses the dose? What to do in such circumstances?

Answer — There are 3 doses of QHPV which has to be administered in the following schedule

- 1st dose – 0 months
- 2nd dose – 2 months
- 3rd dose – 6 months

ALTERNATIVE SCHEDULE

- 1st dose – 0 months
- 2nd dose – 1 month
- 3rd dose – 4 months

As long as all 3 doses are completed in one year it is fine. But it is best to complete the schedule in 0, 2 & 6 months.

Based on the post-hoc analysis, comparable efficacy will get if minimum gap between 1st & 2nd dose is 1 month and that of between 2nd& 3rd dose is 3 months.

For girl's b/w 9 to 14 years – 2 doses 6 months apart is the schedule. If they, miss that schedule then you have to administer 3 doses.

Although approved in many countries – this vaccine is a not approved for usage in Men/Boys in India as of now.

Question : When do I vaccinate. What age group? Which age group is best for vaccination?

Answer — HPV infection is sexually transmitted and is usually acquired within the first few years following sexual debut.Ideally, therefore, the vaccine should be administered before sexual debut, i.e. before any risk of exposure to HPV (age from 9 yrs. till 15 or 16 yrs.). Also, it is important to remember that antibody response to vaccine is much higher in younger age group. Thus, young age (9 to 15-17 yrs) is best age to vaccinate.

However, if one cannot vaccinate young and adolescent girls due to any reason then one must vaccinate at the next available opportunity as the

window period to vaccinate is long (9 to 45 yrs.).

Another opportunity for vaccination is POST PARTUM period as QHPV is found to be safe in this period. There are studies which have indicated that women are also more receptive to the idea of vaccination, hence they listen to their OBGYNs for vaccination.

The whole idea is to improve practice patterns so that clinicians use every opportunity to recommend HPV vaccines and address questions from parents. This can help realize reductions in vaccine-preventable infections and cancers caused by HPV.

In "safe motherhood" programs of India, this vaccination may be included.

Question : What if a woman becomes pregnant after taking the vaccine? Or she was already pregnant and had taken the vaccine?

Answer **—** Vaccination Should NOT be done during pregnancy. The reason is that there not enough well controlled studies done in humans for pregnancy as getting approvals & subjects for studies during pregnancy is difficult.

However, if someone was pregnant or gets pregnant and vaccination does happen there is NO NEED for termination of pregnancy as the studies have indicated that vaccine does not cause any risk of additional fetal malformations or abortions or any harm. However as soon as pregnancy is confirmed the remaining dose/s should be deferred and can be administered after the delivery.

Reference - 6 years pregnancy registry data (Mary Ann Goss, 2014)

Question : Is there any use of protection against genital warts (GW)? I hardly see any cases of GW?

Answer **—** The prevalence of GW as done by a study in India was around 1%.

Another study done in Denmark with a follow up of 30 yrs. involving around 50,000 subjects indicate that **Diagnosis of GW was strongly related to anal, vulvar, vaginal, cervical & sub sites of Head & Neck cancer with confirmed HPV association.** Hence if one can prevent GW then one must.

Question : I do screening regularly. Is screening better & more cost effective than vaccination or is vaccination a better tool?

Answer **—** Ideally both screening & vaccination should go hand in hand. Just because you are screened DOES NOT mean that you don't require vaccination and vice versa.Also, there is no need of doing screening just prior to vaccination.

Thus, it is best to vaccinate as well as follow the guidelines for screening of that country

Question : I understand that vaccination is good, but development of cervical cancer takes almost 10 to 15 years then how we know if the vaccine is going to prevent cancer in say a lady who got vaccinated just now or one year ago.

Answer **—** Since the vaccine was launched in 2006 many countries have adopted it in their NIP (National immunization program) and we are beginning to get good "REAL WORLD EFFECTIVENESS" data from such countries. Ex- Australia, New Zealand, Denmark, Sweden etc.

One recent and interesting data from Australia which is one of the first countries to include QHPV in their NIP indicates -"*With data from a state-based cervical screening register, we have shown a decrease in high-grade cervical abnormalities in young women after the implementation of the vaccination program".*

Also, since GW takes less time to develop as compared to Cancer there has been a substantial reduction in GW in both women & men.

Similarly, we have encouraging data from other countries too.

Question : What about cross protection. I heard that Bivalent offers cross protection against other HPV serotypes namely 31,33,45 etc. whereas QHPV does not?

Answer **—** It is worthwhile to remember that both QHPV & BHPV contains HPV 16 & 18 which are "High risk types" i.e. these are associated with cancer causation especially cervical cancer (Globally 16 & 18 are responsible for causing 70% of all cervical cancer case whereas in India they are responsible for causing around 82% of the cases). Hence, we should be focusing more on the serotypes which are by far predominantly responsible for causing most of the cancers i.e. 16 & 18.

As far as protection against other serotypes is concerned the cross protection with both the vaccines is inconsistent & short lived.

Direct protection & Long term follow up are the best

indicators for protection (NORDIC data with QHPV) rather than cross protection.

Merck has launched GARDASIL 9 (HPV serotypes 6, 11, 16, 18, 31, 33, 45, 52 & 58) this will take care of >90% of the HPV responsible for cancer.However, GARDASIL 9 is as of now not available in India.

Question : Is the vaccine safe? I have read on internet and media about stories doing the rounds? I am a bit concerned?

***Answer* —** There is no denying that the vaccines have attracted a bit of negative publicity. However, it is important to remember that many international bodies like: - USCDC (Centre for Disease control), WHO, EMEA (European medicines agency) have conclusively said that vaccine is safe.

In almost all the cases the complaint filed due to or against the vaccine has not been found to be associated with the vaccine ie, CAUSALITY could not be attributed to the HPV vaccines.

In addition, surveillance is ongoing, and the vaccines will continue to be monitored.

Our own FOGSI & IAP (Indian Academy of Pediatrics) have recommended this vaccine.

One must not pay heed to online rumours.

Question : Is it true that antibody titers with QHPV falls after some time and we might need a booster?

***Answer* —** It is important to note that both QHPV and BHPV induce antibodies and after some years that antibody levels fall. But it is equally important to note that this quantitative estimation of FALL in antibodies has no effect as far as protection against HPV is concerned because the level of antibodies required to provide protection against HPV is not defined. Thus, currently there is no need for any booster.

In addition, instead of going for indirect markers like antibody titers the best indicator of protection is *CLINICAL ENDPOINTS ie, ABSENCE OF DISEASE that is where current NORDIC data of 14 years becomes important.*

Question : I recommend the vaccination to almost everyone yet very few come forward for vaccination. What should I do?

***Answer* —** Studies have demonstrated that the strongest recommendation comes from the physician/ OBGYN/doctor

Some strategies are : -

- Strongly recommend adolescent vaccines to parents of your 9 year and older patients. **Parents trust *your* opinion more than anyone else's when it comes to immunizations.**
- Use every opportunity to vaccinate your adolescent patients. **Ask about vaccination status when they come in for sick visits.**
- **Use vaccine on Postpartum period/Post-delivery –** If the woman has not received HPV vaccination earlier.
- Patient reminder and recall systems such as automated **postcards, phone calls and text messages are effective tools for increasing office visits.**
- **Educate parents about the diseases that can be prevented by vaccines.** Parents may know very little about pertussis, meningococcal disease, or HPV.
- **Implement standing orders policies** so that patients can receive vaccines without a physician examination or individual physician order.

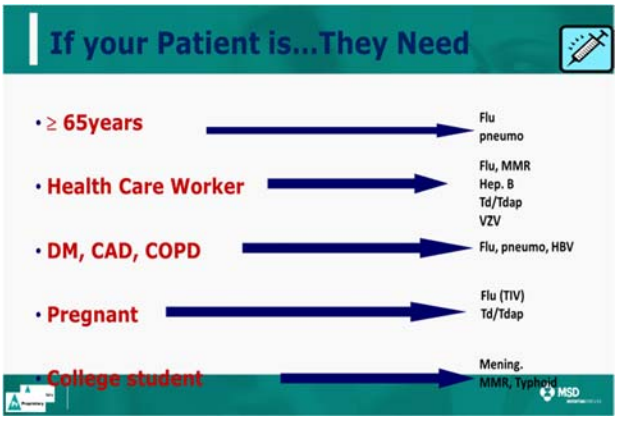
All branches of medical science must come forward for promoting HPV vaccinations.

OTHER QUESTIONS

Vaccination Related :

1. Should Health care workers and doctors also take Pneumococcal and Influenza vaccination during this COVID times?

***Answer* —** yes, everyone should be protected as per their age and indication



2. What will be the pneumococcal Vaccine schedule for a 50+ healthy HCP (Health Care provider)?

Answer — As per the latest ACIP (Advisory Committee on Vaccines and Immunization practices)-2019 guidelines if there is no underlying medical condition ie, person is healthy b/w age of 19 to 64 years no Pneumococcal vaccine is recommended.

3. What is the relevance of Pneumococcal vaccination during this COVID pandemic times?

Answer — As per the NFID (national Foundation for Infectious Diseases)Although there is no vaccine available to prevent COVID-19 at this time, ensure that other vaccinations are up to date, including influenza and pneumococcal vaccines. This will help reduce the pressure on the healthcare system by reducing vaccine-preventable diseases.

Physicians of today must discuss adult vaccinations with their patients. There are many studies which have proved the efficacy of these vaccines in reducing mortality.

For example, Meningococcal Vaccine may be given to imnmates of prisons or crowded hostels to reduce mortality.

Similarly, people going on trekking or jungle safaris must take Typhoid Vaccine.

Thank you Dr. A. Muruganathan for your answers. We appreciate the time taken by you and we are sure that our readers will be benefited immensely.

VACCINE TABLES

RECOMMENDED VACCINATION SCHEDULE FOR HEALTHY ADULTS

Vaccine	Recommended age of vaccination
Influenza (flu)	Yearly
Tetanus, diphtheria (Td) Or Tetanus, diphtheria, pertussis (Tdap)	Td every 10 years Replace one dose with Tdap
Varicella (chickenpox)	Two doses (unless had documented disease or immunized as a child or adolescent)
Human papillomavirus (HPV)	Three doses before 26 years of age (unless already immunized as an adolescent)
Measles, mumps, rubella (MMR)	One or two doses (uless immunized previously with two doses after the age of 1 year, known to have been previously infected)

VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS

	Pregnancy	Splenectomy	Diabetes	Kidney disease and hemodialysis	Heart disease, lung disease and chronic alcoholism	HIV	Liver disease
Influenza	Yes	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults
Tdap	One dose for every pregnancy	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults	Similar to healthy adults
Hepatitis B	If there is no immunity	-	Yes	Yes	-	Yes	Yes and Hepatitis A if no immunity
Pneumococcal vaccine	-	PCV 13 PCG 23	PCV 23 (Preferred)	PCV 13 PCV 23	PCV 23 (Preferred)	PCV 13 PCV 23	PCV 23 (Preferred)
Meningococcal vaccine	-	Either conjugated or polysaccharide	-	-			-
Haemophllus influenza type B		One dose	-	-	-	-	-

VACCINATION FOR HEALTHCARE WORKERS

Influenza	One dose annually
T dap	Simimar to healthy adults
Hepatitis B	3 doses if no immunity followed by booster dose once in 5 years
Varicella	Two doses (unless had documented disease or proof of immunity)
MMR	One dose at the time of joining health care job
Typhoiod	For food handlers in the hospital kitchen and microbiology laboratory personnel once in 3 years

VACCINE TABLES

TRAVEL VACCINATION

	Visitors travelling India	Indians travelling to USA	Travel vaccines
Typhoid	2 weeks before the travel		
Hepatitis A	2 weeks before the travel		
Hepatitis B	2 months before travel	Similar to healthy adults	
Rabies	3 doses (0,7,21) 1 month before travel		
Japanese B encephalitis	2 doses at 4 week interval, 1 month before travel		
Influenza	1 dose annually	1 dose annually	
Tdip		Students and visitors above the age of 65 years going to handle children	
MMR		One or two doses for students going for higher sudies	
Polio			Travelers to Afghanistan, Cameroon, Equatorial Guinea, Ethiopia, Iraq, Israel, Nigeria, Pakistan, Somalia and Syria
Meningo-coccal vaccine		One or two doses for students goting for higher studies	To persons going for Haj pilgrimage
Yelow fever			Africa : Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Coted' Ivoire, Domocratic Republic of Congo, Equatorial Guinea, Ethropia, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leona, Sudan, South Sudan, Togo, Uganda **South America :** Argentina, Bolivia, Brazil, Colombia, Ecuador, French, Guyana, Guyana, Suriname, Trinidad (Trinidad only), Venezuela, Panama, Paraguay, Peru

Original Article

The Glitch with the Web of Anti Tubercular Drugs — A Prospective Study on Adverse Drug Reactions

Santanu Kumar Ghosh[1], D P Singh[2], Abhishek Kumar Tiwari[3], Ajay Kumar Singh[4]

Adverse drug reactions to antituberculous drugs in DOTS are common and can cause significant morbidity and mortality. Gastrointestinal intolerance, hepatitis and cutaneous side-effects are commonly encountered. Early recognition and treatment will prevent the problem of drug non-adherence.

Background : As to the contour of adverse drug reactions (ADRs) due to directly observed treatment, short course, there is very little compiled data of patients receiving anti-tuberculosis (anti-TB) chemotherapy in Bhagalpur, Bihar, India. One of the main reasons for non-adherence, modification or discontinuation of anti-TB therapy (ATT) is ADRs, even under DOTS.

Aims : This study intended to conclude the frequency of ADRs due to DOTS therapy with a TB population of Bhagalpur, India.

Design : A prospective cohort study, and performed during July 2017-December 2018.

Materials and Methods : The study incorporated 108 diagnosed TB patients on anti-TB treatment under DOTS. Every patient was followed-up for the extent he/she received the treatment. Statistical Analysis: Frequency of different ADRs was assessed and p value was determined.

Results : Incidence of TB was more among males than female (73% against 27%). 65% showed one or more ADR. Incidence of ADRs based on affected organ was: Gastrointestinal (GI) disorders in 40 patients (57%), generalized weakness in 12 patients (17%), liver dysfunction in 11 patients (15%), allergic skin reactions in 5 patients (7%), neurological system disorders in 1 patient (1%), and fever in 4 patients (5%). However, 35% did not experience any ADRs.

Conclusion : Frequency of ADRs due to DOTS therapy was 65%. Majority of cases suffered from GI symptoms. This decorated the significance of mounting strategies to improve ADRs both to improve the quality of patient care and to control TB safely.

[*J Indian Med Assoc* 2021; **119(1):** 43-6]

Key words **: Revised National Tuberculosis Control Program (RNTCP), Directly Observe Treatment Short Course (DOTs), Anti Tuberculous Drugs (ATT), Adverse Drug Reactions (ADRs).**

Neolithic Old Disease :

Tuberculosis has afflicted the whole human race since time immemorial; this presumption has been confirmed by the fact that tuberculosis lesions have been found in mummies of Neolithic man dating back to 3700 BC[1]. M tuberculosis is transferred from a person harboring it via aerosolized unit of infection, better known as 'droplet nuclei'. The purpose of breaking the nuclei into tiny aerosols is performed by coughing, speaking, singing, sneezing or any other respiratory maneuvers. The size of the infecting speck has got clinical significance because the smaller particulates are competent of sneaking into the alveolar surface whereas the larger ones are caught red handed and cleared by the mucociliary shipping. It has been demonstrated in the smaller mammals that most of the bacilli inhaled as a solitary unit reaches the alveolus and form a tubercle, on the other hand it is highly unlikely that more than a single organism, gets deposited at any one site[2,3]. The problem with the droplet nuclei, which are often 5 μm in diameter, is that once they are dispersed they seldom settle soon and they remain viable for an extended time interval[4].

Editor's Comment :

- **Frequency of ADRs due to anti-tuberculous drugs in DOTs therapy was 65% in this study.**
- **Majority of the patients suffered from GI symptoms, Hepatic dysfunction, Fever and allergic reactions.**
- **Most of ADRs are mild in nature but some may warrant hospitalization.**
- **Early recognition and mounting strategies to improved ADRs will improve not only the quality of patients care but also help in National Tuberculosis Elimination Program (NTEP).**

JLN Medical College & Hospital, Bhagalpur 812001

[1]MD, DTCD, FICP, Associate Professor, Department of TB & Chest

[2]MD, DTCD, FICP, FACP, FIAMS, FCSI, FICS, FRCP, Professor & Head, Department of Respiratory Medicine and Corresponding Author

[3]MBBS, MD, Senior Resident, Department of Medicine

[4]MD (Medicine), Medical Officer, Department of Respiratory Medicine

Received on : 08/07/2020

Accepted on : 22/07/2020

Contrary to the popular belief, these nuclei traverse the simple masks. Even covering the mouth and nose during cough doesn't avert it from dispersal.

Modern Weapons :

Directly observed treatment, short course (DOTS) was brought against the face of Tuberculosis in India in 1993 as part of Revised National Tuberculosis Control Programme (RNTCP), subsequent to an appraisal of India's NTP a year earlier[5]. The key components of DOTs comprise of directly observed treatment of TB by thrice weekly doses of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), and/or Streptomycin (SM) for a duration of 6-9 months[6].

Studies have shown that anti-tuberculous may cause many uninvited side effects like hepatic dysfunction, GI side effects, rashes, neuropathy and many ADRs[7-11]. Studies propose that 1 out of 20 patients on anti-tubercular drugs (ATT) develop ADRs[12,13]. Not even a single anti-TB drugs is devoid of unfavorable reactions, although only seldom are the adverse reactions grave. ADRs can be a impending factor leading ill fitting compliance[14]. ADRs substantiates patient anguish and invite considerable burden to the patients and some may need hospital admission. The aim of this study is to make a review of ADRs caused by Anti-tuberculous Therapy.

Materials and Method

Study Design and Sample Selection :

This observational prospective study was undertaken in the Department of Respiratory Medicine, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar from July 2017 to December 2018. We obtained the proper approval from the Institutional Ethical Committee. The study included 108 successively diagnosed patients of pulmonary or extra-pulmonary Tuberculosis attending our outpatient facility. The patients were chosen without the constraints of age, sex, and race. Those patients who were simultaneously being treated for some other ailments were barred from being part of our study. Those who were transferred, or those who deserted the treatment regimen, and those whose diagnosis was changed during the course of the treatment, and succumbed due to other illness during the monitoring were also disqualified.

Investigation and Follow-up :

Before starting the ATT, participants selected accomplished the baseline feedback form. The laboratory investigation included Complete Blood Count (CBC), Routine urine test, liver and renal function test, base line ECG and serum electrolyte. During the follow-up laboratory investigations were repeated 2 months after commencement of DOTs Therapy. The patients were asked to use a diary to self-record any unpleasant reactions and to report to the Medical College Outpatient Clinic. Once an alleged adverse reaction was reported it was recorded by treating physicians and follow-up was done till the completion of the course. ADR patients had their therapy tailored according to their side effect profile. Follow-up was done every fortnight to all patients during the full duration of DOTs.

Unwanted Reactons :

ADRs are considerably damaging or obnoxious reaction, consequential to an intervention connected to a drug, which predicts vulnerability from future use needing prevention, dose change or withdrawal of the product. ADRs and the timing of their appearance during treatment, as well as subsequent modifications in the treatment regimen, were noted[15].

Sternness of the ADRs was classified according to Hartwig *et al*[16], as: mild, moderate and severe.

(i) Mild ADRs were self-limiting and resolved without any treatment.

(ii) Moderate ADRs were reactions which required treatment resolving within a day. and

(iii) Severe ADRs were those that were life-threatening illness needing urgent hospitalization or intensive care management or even death of patients.

Results

73% Patients in our study were males, whereas 27% were females. 65% of those getting the anti-tubercular therapy were associated with some side effects.

Incidence of ADRs by DOTs therapy has been exhibited below in Table 1.

The unwarranted drug reactions occurred more amongst the younger population group with a maximum incidence amongst ≤25 years old and those above 50 years of age were least affected. This variance in ADRs amongst the dissimilar age groups was significant statistically (P 0.001). Although females comprised of only 27% of our study population, the preponderance

Table 1 — *Showing ADR based on Body Systems*

ADR based on Body Systems	No of Patients	% age of ADR
Gastrointestinal (GI) Symptoms	40	57%
Generalized Weakness	12	17%
Hepatitis	11	15%
Cutaneous Drug Rashes	5	7%
Neuropathy	1	1%
Pyrexia	4	5%
No ADRs	35	0%

of adverse reactions was more in the female TB patients as compared with the males (86% against 63%) and this difference was again statistically significant (P 0.001).

Discussion

The most primitive recorded human case of tuberculosis dates back to almost 9000 years. Early treatment modalities, such as bloodletting, were replaced by infirmary regimens in the late nineteenth century. The unearthing of Streptomycin in mid 19th century launched the epoch of antibiotic treatment for TB. Over ensuing decades, the discovery of supplementary agents and the use of multiple- drug regimens permitted progressive curbing of the treatment course from years to as little as 6 months for drug-susceptible TB. Latent TB infection and active TB disease are diagnosed by history, physical examination, radiographic imaging, tuberculin skin test, interferon γ release assays, acid-fast staining, mycobacterial cultures, and/or new molecular diagnostics.

Adherence to medications is significant in achieving a cure with anti- mycobacterial therapy. In addition to directly observed therapy by trained staff, case management interventions such as education/ counseling of patients, field/ home visits, and patient reminders are also recommended to improve treatment adherence. The use of mobile based health technologies including videos, messaging, electronic pillboxes etc, show assurance in promoting adherence to treatment. In susceptible TB, monthly administration of TB medications is also advocated to permit indispensable clinical monitoring for hepatotoxicity due to these.

Monitoring includes at least monthly appraisal for symptoms (queasiness, vomiting, GI discomfort, and inexplicable fatigue) and signs of hepatotoxicity including jaundice. The existence of such symptoms and signs mandates interim discontinuation of potentially hepatotoxic agents; discontinuation at the onset of hepatitis symptoms curtails the risk of progression to life threatening hepatic derangments. Biochemical testing of at least Serum Glutamic Pyruvic Transaminase (SGPT) and total bilirubin levels and segregation of other causes of these abnormalities are also indicated during treatment for those at risk for hepatotoxicity.

Our study was planned to find out the adverse reactions of ATT among the TB patients presenting to our hospital. The males compose the chief population of the study, that is, 73% males against 27% females. Males are the favorites for acquiring the disease pertaining to their higher risk factors like smoking, alcoholism and drug addiction. In addition the male are socially more malleable then the female counterpart[17]. It has been established that tuberculosis was more widespread in the age group of 25- 45 years. Edoh and Adjei also instituted high frequency in the age group of 21-40 years with the highest peak of 29% in the group of 31-40 years[18]. This, in all probability, is for the reason that the people in this age group are involved in TB infectious activities resulting in the deteriorating immunity[19].

The preponderance of TB cases was 59% with the weight of ≤55 kg and 41% in body weight of 55 kg body weight. In the study done by Iyer *et al*, TB patients (80%), weighed underneath standard for Indian reference adult man[20]. These patients often experience severe weight loss, a symptom that is considered immunosuppressive and a major determinant of ruthlessness of the disease[21]. Undernourishment is an imperative risk factor for TB, since cell- mediated immunity is the key host defence against TB.

The most common unwanted drug reaction was those of GI symptoms (57%) mostly caused by rifampicin and pyrazinamide. 15% patients developed hepatic dysfunction. The drugs that are responsible for this side effect may be H, R & Z[22]. 7% patients experienced allergic skin reactions. In the present study, 35% did not experience any ADRs. Most of the reactions were of milder degree not requiring any specific interventions or hospitalizations but a few others warranted the discontinuation or tailoring of the drugs being used for treating the disease. Although GI symptoms were the most common unwanted effects which on most occasions were annoying and discomforting, they seldom encouraged the discontinuation of ATT.

Limitations :

Sample size in our study was small, although its findings show similarity with national data. Large population study will provide better composite picture of ADRs.

Conclusion

Local Story In Global Framework :

Our study population although diverse in composition and cultural values, it showed similarity with the national data in the demographic and epidemiological values. The males were found to be more caught in hand by the M. tuberculosis, females were less adversely affected but the ATT was found to be harsher to them and the younger ones giving them more frequent side effects. The side effect profile being the major determinant in the adherence to the prolonged regimen, our study gave better insight into the side

effect profile of demographic zone of Bhagalpur, Bihar.

Funding : None.

Conflict of Interest : None.

Ethical permission : Taken.

References

1 Morse D, Brothwell DR, Ucko PJ — Tuberculosis in ancient Egypt. *Am Rev Respir Dis* 1964; **90:** 524.
2 Ratcliffe HL — Tuberculosis induced by droplet nuclei infection. *Am J Hyg* 1952; **55:** 36.
3 Ratcliffe HL, Palladino VS — Tuberculosis induced by droplet nuclei infection: initial homogeneous reponse of small mammals(rats, mice, guinea pigs and hamsters) to human and to bovine bacilli, and the rate and pattern of tubercle development. *J Exp Med* 1953; **97:** 61.
4 Wells WF — On airborne infection II. Droplets and droplet nuclei. *Am J Hyg* 1934; **20:** 611.
5 Balasubramanian VN, Oommen K, Samuel R — DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India. *Int J Tuberc Lung Dis* 2000; **4:** 409-13
6 World Health Organization — An expanded DOTS framework for effective tuberculosis control. Stop TB Communicable Diseases. Geneva: WHO Press; 2002. p. 1-20.
7 Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D — Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003; **167:** 1472-7.
8 Vieira DE, Gomes M — Adverse effects of tuberculosis treatment: Experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. *J Bras Pneumol* 2008; **34:** 1049-55.
9 Zaka-Ur-Rehman Z, Jamshaid M, Chaudhry A — Clinical evaluation and monitoring of adverse effects for fixed multidose combination against single drug therapy in pulmonary tuberculosis patients. *Pak J Pharm Sci* 2008; **21:** 185-94.
10 Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, *et al* — Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis* 2007; **11:** 868-75.
11 Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR — Study of adverse drug reactions caused by first line anti-tubercular drugs used in directly observed treatment, short course (DOTS) therapy in Western Nepal, Pokhara. *J Pak Med Assoc* 2008; **58:** 531-6.
12 Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK, Shadab K, Jain SK — Adverse drug reactions observed during DOTS. *J Commun Dis* 2004; **36:** 251-9.
13 Chukanov VI, Kaminskaia GO, Livchane E — Frequency and pattern of adverse reactions due to treatment of patients with pulmonary tuberculosis with antitubercular reserve drugs. *Probl Tuberk Bolezn Legk* 2004; **10:** 6-10.
14 Awofeso N — Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bull World Health Organ* 2008; **86:** B-D.
15 Edwards IR, Aronson JK — Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000; **356:** 1255-9.
16 Hartwig SC, Siegel J, Schneider PJ — Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992; **49:** 2229-32.
17 Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C — Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008; **8:** 289.
18 Edoh D, Adjei R — Rapid assessment of a National Tuberculosis (TB) Control Programme in Eastern Ghana. *Afr J Health Sci* 2002; **9:** 159-64.
19 Horne N — Tuberculosis and other mycobacterial disease. In: Cook G, editor. Manson2 s tropical diseases. London: W.B. Saunders; 1996. p. 971-1015.
20 Iyer SP, Umakumar K, Mahajan A — Impact of HIV Infection on utcome of abdominal tuberculosis. *Bombay Hospital J* 2008; **50:** 553-9.
21 van Crevel R, Karyadi E, Netea MG, Verhoef H, Nelwan RH, West CE, *et al* — Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. *J Clin Endocrinol Metab* 2002; **87:** 758-63.
22 Steele MA, Burk RF, DesPrez RM — Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* 1991; **99:** 465-71.

Evaluation of DOTS Therapy and Indian Policy

India is one of the highest TB burden Countries accounting for one fifth of incidence of TB. Directly Observed Treatment, short course (DOTs) started a India in 1993 as a part of Revised National Tuberculosis Control Program.

DOTs involves free diagnosis of TB and free full six months treatment. The patient needs to visit TB clinic thrice a week in first couple of months and then once weekly during continuous phase.

Thus in DOTs patients adheres to complete duration of treatment and reduces the chances of Drug Resistance TB.

Although Government policy is to notify and treat 70% of all TB cases but notification and cure rate is far from satisfactory

High priority is needed to improve the quality and reach of DOTs services in the country.

Patients treated outside the DOTs strategy needs to be minimized to reduce incidence of Resistant TB.

In order to achieve universal access to the program government should engage the private sector to achieve the goal of NTEP (National Tuberculosis Elimination Program).

In start of year 2020, RNTCP was renamed as NTEP which had the aim to achieve the larger goal of elimination of the disease of tuberculosis by 2025.

Original Article

Faculty Perceptions of Theory Question as an Assessment Tool : A Survey

Anjan Adhikari[1], Santanu Munshi[2], Moumita Roy[3], Sangita Bhattacharya[4], Rania Indu[5], Anup Kumar Das[6]

Background : Medical Education is recognized as an essential system for ensuring the quality of health of common people. Assessment plays a very important role in guiding the direction of the development of meaningful learning. Theory question paper is a tool for the evaluation of medical students. Theory questions should be properly framed for meaningful learning.

Method : A survey was conducted among the teachers/faculty members of a Medical College in Kolkata, West Bengal, India, to evaluate the knowledge and perception of the faculty members on important aspects related to the framing of theory question papers for undergraduate medical student's assessment. The knowledge and perception of the faculty members were explored using a pre-designed, pre-coded, pre-tested, questionnaire with both closed and open ended questions. In the present study, perception regarding framing of theory questions for assessment was collected from 41 faculties from different Departments.

Results : Most of these participants (31.7%) belonged to the age group of 51 to 60 years. Sex distribution revealed a male predominance(60.9%). 52.5% of the faculty were found to be using a blueprint for framing a question paper for the theoretical assessment of the students. The faculty also opined that there is a definite need of Faculty Development Program (FDP) on framing of theory questions.

Conclusion: Present study explored different important facets of assessment through framing of theory questions. Such studies are required to strengthen the assessment system. This helped in ensuring the objectives of education with effective learning.

[*J Indian Med Assoc* 2021; **119(1):** 47-51]

Key words **: Assessment, Theory Questions Faculty Development Program (FDP), Learning.**

Medical education is the curriculum of education for medical students or medical practitioners. In this modern era, medical science is changing every moment with discoveries and inventions. Regular modification of this course is thus essential to incorporate the newer developments, newer understanding, etc. Educated and skilled teachers are thus essential to train future clinicians. Assessment is an essential part of medical education. Assessment is the key motivator to learn and thus appropriate assessment tool is required to evaluate the performance of the medical students[1].

Editor's Comment :

- **Most of the faculty opined that theory questions should cover the learning objectives of the syllabus.**
- **The theory questions should evaluate the interpretation skill of the students.**
- **The faculty also suggested that the question paper should be based on "must know", "useful to know", and "nice to know" areas.**
- **A blueprint is essential for framing a question paper for the theoretical assessment of the students.**
- **The faculty were also aware of the significance of Faculty Development Program (FDP) for framing theory questions.**

Assessment method can be of two different types; summative assessment and formative assessment. Summative assessment usually occurs at the end of a particular module or course. It focuses on the outcome of a program. It summarizes a student's progress at the end of a particular term. It helps to underst and whether the academic objectives set for a particular course has been achieved or not. Summative assessment is a reflection of cognitive achievements commonly. It is the most primitive method of assessment practiced throughout the world[2].

Formative assessment is, on the other hand, defined as "a wide variety of methods that teachers

[1]MBBS, MD (Pharmacology), Professor and Head, Department of Pharmacology, Coochbehar Government Medical College, Coochbehar 736101

[2]MBBS, MD (Pharmacology), Professor and Head, Department of Pharmacology, Calcutta National Medical College, Kolkata 700014 and Corresponding Author

[3]B Pharm, M Pharm, PhD, Assistant Professor, Department of Pharmaceutical Science, JIS University, Kolkata 700109

[4]B Sc, M Sc, M Tech, PhD, Research Scholar, Department of Bioscience and Engineering, School of Bioscience and Engineering, Kolkata 700032

[5]B Tech, MS, PhD, Research Scholar, Department of Bioscience and Engineering, School of Bioscience and Engineering, Kolkata 700032

[6]MBBS, MD (Pharmacology), Principal, Lord Buddha Koshi Medical College, Saharsa 852201

Received on : 08/07/2020
Accepted on : 22/07/2020

use to conduct in-process evaluations of student comprehension, learning needs, and academic progress during a lesson, unit, or course"[3]. It motivates teacher-student interaction. It provides valuable feedback that helps the tutors to identify the students' learning capability and improvise their teaching skills. This type of assessment encourages a dynamic learning process, helps to identify the strength and weaknesses of students and improves the quality of teaching[4]. A longitudinal cohort study among undergraduate students of Caribbean Medical School showed significant improvement in academic performance of students after implementation of formative assessment while teaching[5]. Formative assessment with appropriate tool was also developed to enhance the learning skill in medical students of LN Medical College, Bhopal, India[6].

A hierarchical model for the assessment of clinical competence was proposed by Miller in 1990[7]. According to this model, assessment of cognitive skill precedes the assessment of behavior & skill in practice. Professional authenticity improves from the base to the top of the model. Assessment of cognition comprises of knowledge and its application. Competence in controlled conditions, in practice, is evaluated by assessment of behavior. Several assessment methods are thus employed to achieve the learning goal. Each method has its advantages and limitations. Thus, the employment of more than one method has proved to be useful in achieving the learning objectives[8]. Various methods & tools are introduced to evaluate the student's understanding, knowledge, and competency about a course[8,9]. Few of these include:

- Written examination- This is an old method of evaluating pupil's cognitive skills.

♦ Long essay questions are given to evaluate complex learning situations. These questions are essential when the student tries to summarize, describe, or provide information about a new situation. They require more time to answer. This helps to evaluate the recall capacity of a student.

♦ Modified Essay Questions (MEQs) comprise a case followed by a series of questions, pertaining to the case. This type of question is essential to evaluate a student's problem-solving capacity, reasoning skill, understanding of a concept, and capacity to apply the knowledge.

♦ Short Answer Questions (SAQs) comprise unambiguous open-ended questions that require an answer in one or two words/sentences.

♦ Multiple Choice Questions (MCQs) requires the candidate to select one best answer from three or more options. These types of questions evaluate the cognitive, reasoning, understanding, problem-solving, and application skill of the student.

- Oral Examination/Viva: It is based on student-teacher interaction. Often this method has biasness and thus need to be implemented carefully.
- Objective Structured Clinical examination (OSCE) is a method to evaluate the clinical skills of a student. In this test, student is asked to conduct multiple tasks at a number of 'stations'. It helps to estimate various aspects of the student's clinical competence. OSCE also evaluate all the three domains.
- Mini-Clinical Evaluation Exercise (Mini-CEX) is a rating scale implemented by the American Board of Internal Medicine to assess six core competencies of physicians: medical interviewing skills, counselling skills, physical examination skills, clinical judgment, humanistic qualities/professionalism, organization, and efficiency.
- Direct Observation of Procedural Skills (DOPS) is a structured rating scale for judgment of technical skills and practical procedures.

In the theoretical examination, it is the sole responsibility of the faculty/assessors to frame a rational, and effective question paper that can correctly assess the performance of the students, highlight the understanding of the subject and in turn, give valuable feedback of the learning process. Examiners need to evaluate the course contents and frame questions based on the area of importance according to must now, nice to know, and desirable to know. Proper marks distribution needs to be provided following the norms of Universities. There are very few studies that investigate the skill and quality of medical teachers to frame effective question papers for theory examination. Hence, evaluation of knowledge and perception of faculty in framing theory question papers for assessment of medical education is the need of the hour. It is also essential, at the same time, rational to implement faculty development programs to train and improve the skills of the faculty so that they can prepare a justified question paper.

Materials and Methods

Study Type : Questionnaire-based survey

Study Duration : The study was carried for a period of six months from December 2018 to May 2019

Place of Study : Department of Pharmacology.

Study Population : Medical education faculty under West Bengal University of Health Sciences were included in the study following the inclusion criteria and their willingness for participation. Study population comprised of faculty from different Departments of the Medical College.

Inclusion Criteria :

- Faculty, participating in the preparation of theory question papers for undergraduate students' summative theory assessment for college or university

- Minimum qualification : Postgraduate in the discipline
- Minimum 2 years of teaching experience

Exclusion Criteria :

- Faculty who were directly involved with the study

Ethical Clearance : Ethical clearance was obtained from the Institutional Ethics Committee.

Study Design : The preparatory phase of the study included the preparation of the questionnaire, its pre testing. Later on a survey was done on the predesigned, pre tested, pre coded questionnaire for evaluating the perception of the teachers for framing of questions for theory assessment. So, it is a questionnaire based cross sectional survey.

Statistical Analysis : All the data will be entered in Microsoft Excel 2010®. The data was calculated by using the Statistical Package for Social Sciences Software 21.0 (SPSS)®.

Results

Primarily 41 responses were collected from facultys of different departments, pre and para-clinical (30) and clinical (11). As per age groups of study population, the maximum number belonged to the age group of 51 to 60 years, ie, 13 (31.7%), followed by 31 to 40 years, 26.8 %, with a male predominance, ie, 60.9% (25) and faculty belonged to undergraduate study (22, 55%). Faculty was categorized according to the length of examinership completed in years at university level. Out of the total respondent of this question (n=23), the maximum population has experience as examiner is between 5 to 10 years, 9 (39.1%), followed by below 5 years and above 10 years, nearly the same. Regarding the training status of faculty, 21 (56.7%) had basic Medical Education training, recognized by Medical Council of India (MCI). Out of the trained faculty (n=21), maximum was trained within 5 years, 12 faculty (57.1%).

Fig 1 revealed the perception of the faculty on whether theory questions should cover the learning objectives of the syllabus. 23 (56.09%) faculty strongly agreed to the fact that the learning objectives should be covered in the theory questions whereas only 2(4.87%) faculty (n=41) strongly disagreed with this notion.

Fig 2 revealed the perception of faculty on different aspects of students' knowledge to be evaluated in theory examination. Most of the faculty 35 (85.36%) opined that theoretical assessment should be such that the interpretation skill of the student can be evaluated. Assessment of the student's knowledge based on theoretical examination relies greatly on the questions and the ease of the language in which the questions have been set. Almost all of the faculty supported (46.34%-Strongly agreed, 46.34%- agreed) with this opinion.

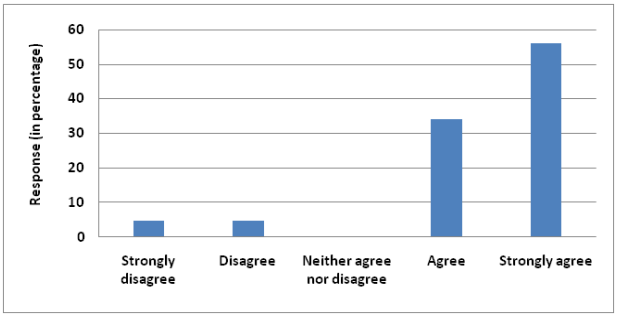


Fig 1 — Perception of faculty on the issue of "Theory Examination Questions' should cover the learning objectives of the syllabus"

"For a theory assessment paper to be valid, it should match course content, have a proportional weighting of content according to clinical importance, consist of questions which are neither overly difficult nor easy and have multiple tools to determine various types of information". To this statement, 20 facultys (48.78%) and 18 faculty (43.9%) were in agreement with the fact that the validity of a question paper depends on multiple tools to determine proper students' assessment.

Table 1 evaluated the perception of faculty on types of questions to be included in the summative assessment for better assessment of the students, 39 (95.12%) and 33 (80.49%) faculty opined that the questions should be "Problem-based" and "justify with answer".

Regarding the opinion of faculty on area of Questions, 23 (56.1%) faculty agreed to the issue that the question paper should be based on "must know", "useful to know" and "nice to know" areas whereas 18 (43.9%) of the study population opined that the question paper should be framed only on "must know" and "useful to know" areas.

Maximum of the faculty came in agreement (Agree- 58.54% and strongly agreed- 29.27%) that use of a blueprint helps in defining a purpose and scope for determining the content of the question paper (Fig 3).

Table 1 — *Perception of faculty about "Types of Theory questions to be included in the summative theory assessment"*

Perception of faculty on "Types of Theory questions"	Number of Participants (n= 41)	Percentage (%)
Essay type (EQ)	5	12.20
Short EQs	12	29.27
Problem based question	39	95.12
Short notes	19	46.34
Short answer questions (SAQ)	24	58.54
Justifying the given statements	33	80.49
Traditional True/False	6	14.63
Multiple choice questions (different types)	23	56.10
Briefly describe the mechanism of action	22	53.66
Any other suggestion	5	12.20

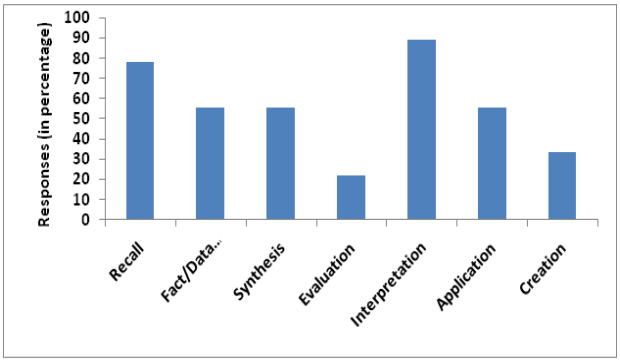


Fig 2 — Perception of faculty on 'Evaluation of different aspects (eg, recall, synthesis, interpretation) of student knowledge' in the theory assessment

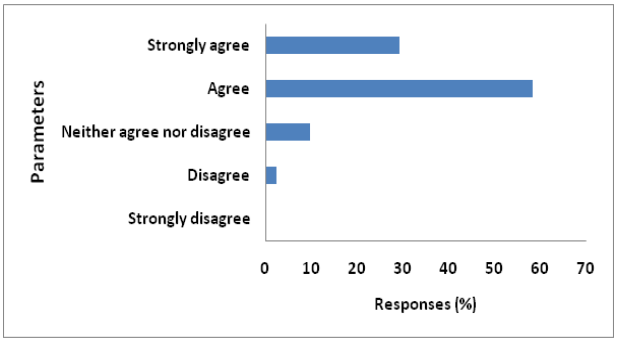


Fig 3 — Perception of faculty on the statement "A blueprint provides a systematic multi-step approach to an assessment, defining the purpose (eg, formative/summative and written/ practical) and scope (eg, for undergraduate or postgraduate students) of the test to subsequently determine content and method of assessment"

83.33% (30) of the faculty suggested that use of a blueprint helps in framing a well-organized question paper 26 (72.22%) and 22 (61.11%) of the faculty suggested that by proper use of blueprint "Students can be tested on different cognitive domains" and "makes the assessment more objective" respectively.

Faculty expressed their opinion on the repetition of previous year theory questions. Some faculty responded that "important questions should be repeated". Some responded that "Topics may be repeated with different clinical problem-based questions." 100% of the faculty responded that marks allotment in a long question should be divided into several components with specific scoring for individual parts. In response to the issue, it is necessary for a student to get 50% marks in theoretical paper alone to get through the examination and 65.85% (27) of the total respondents went on with this notion. Few faculty who disagreed with the above issue opined that "cut off marks should be variable according to the scenario" or pass marks should be 40% or "practical performance should be evaluated before deciding whether the student would fail".

On requesting suggestions for improvement of assessment in undergraduate medical theoretical examination, some faculty came up with new suggestion and ideas like "OSCE may be included", "Extended Multiple Questions (EMQ) to be introduced", "Applied aspect should always be kept in mind prior framing every single question", etc.

Discussion

Education is the process of acquisition of knowledge. It is the pillar of the development and progress of society. Education can be achieved through the teaching and learning process. The tradition of transfer of knowledge from teachers to students is practiced since times immemorial. Assessment has become an inevitable part of the process of teaching-learning. It helps to motivate the students to learn, increases the understanding of the students, and also provides valuable feedback on the process of teaching[10].

Knowledge and perception of faculty were estimated in the present study through a questionnaire survey. The mean age of the faculty in the study was 44.56 ± 1.68 years. Male predominance of about 60.9% was observed. A similar study in a Medical College in West Bengal, India, showed the average age of the study population was in between 38-64 years, where it was observed that 87.5% was male[11]. Most of the faculty (55%) participated in the study used to teach at the undergraduate level. Faculty development program (FDP) in India is gaining momentum these days. Present study showed 56.7% had training in Medical Education technology. Literature had shown that the number of medical education units has also increased significantly, since 1997, in India[12]. Present study estimated 64.1% of the faculty were keen to join FDP to improve their teaching skills.

Assessment not only helps to evaluate the understanding of the students but also assists the teachers in revising their teaching method in order to achieve the goal of the learning[13]. Thus it is essential to design the theory assessment paper in such a manner that the learning objectives are covered. Present study revealed that 56.09% of the faculty strongly agreed to the fact that the learning objectives should be covered in the theory questions. Most of the faculty in this study opined that the theory paper should be such that, at least, the interpretation, application of cognitive skills of the students can be assessed. A cross-sectional study among undergraduate students in Iran revealed that critical thinking ability of medical students needs to be improved through the process of assessment[14].

Faculty of the study suggested that more weightage should be given to the questions, which improve the problem-solving skills of the students. Literature

suggested problem-based learning methods have improvised medical education and is practiced successfully in various Medical Colleges in America[15]. 56.1% of the participants in the present study opted that questions should be framed based on "must know", "useful to know" and "nice to know" areas, mostly focusing the "must know" area.

Blueprint is a map and a specification for an assessment program that ensures that all aspects of the curriculum are covered by assessment programs over a specified period of time. In medical education, blueprint helps to associate assessment with learning objectives. Content of assessment is said to be valid when it is congruent with the objectives and learning experiences, and congruence between these pillars of education can be facilitated by using blueprinting in assessment[16]. Faculty in the Department of Pathology in a Medical College in Karnataka, India, perceived that blueprinting should be an integral part of the process of assessment[2]. In the present study, 52.5% of the total study populations were found to be using a blueprint for the preparation of framing a question paper for theoretical assessment. Present study also reflected that faculty agreed to the fact that blueprint is essential in the assessment process.

Limitations :

(1) Due to time limitations only 41 responses were collected from faculty of different Departments, so the sample size was limited and could have been increased to improve the power of the study.

(2) Also to form better opinion the data should have been collected from faculty of more Medical Colleges both Government and Private ones.

(3) The faculty included should also have adequate training and experience in medical education for atleast more than 5 years as University Examinership and of 3 or more different Universities.

(4) It was also very difficult to cover all important topics within the short time span.

(5) Very few studies are available on this topic of "Framing theory questions for assessment of undergraduate students". So, proper comparison of the study data with national and international data was not sufficient.

Conclusion

The question framing skill of the faculty ultimately reflect the quality of the system. Present study revealed that the medical faculty were aware of structuration, learning objectives, and areas of importance and blueprinting in framing theory questions. Faculty Development Program is essential for improvements in different attributes for development of skill of faculty for better assessment.

Finally the UG & PG medical students expectations and demands of such theoretical assessment could have been included.

Prior Publication : Nil.

Permissions : Ethical permission taken.

Financial Support and Sponsorship : Nil.

Conflicts of Interest : There are no conflicts of interest.

References

1 Basheer A — Impact of assessment of medical students in India on assuring quality primary care. *Australas Med J* 2015; **8(2)**: 67-9.
2 Summative Assessment- https://www.edglossary.org/summative-assessment/ (accessed Dec 18, 2018).
3 Formative Assessment- https://www.edglossary.org/formative-assessment/ (accessed Dec 18, 2018).
4 Abu-Zaid A — Formative assessments in medical education: a medical graduate's perspective. *Perspect Med Educ* 2013; **2(5-6)**: 358-9.
5 Arja SB, Acharya Y, Alezaireg S, Ilavarasan V, Ala S, Arja SB — Implementation of formative assessment and its effectiveness in undergraduate medical education: an experience at a Caribbean Medical School. *MedEdPublish* 2018; **7(2)**: 63.
6 Jain V, Agrawal V, Biswas S — Use of formative assessment as an educational tool. *J Ayub Med Coll Abbottabad* 2012; **24(3-4)**: 68-70.
7 Miller GE — The assessment of clinical skills/competence/performance. *Acad Med* 1990; **65(9)**: S63-7.
8 Al-Wardy NM — Assessment methods in undergraduate medical education. *Sultan Qaboos Univ Med J* 2010; **10(2)**: 203-9.
9 Tabish SA — Assessment methods in medical education. *Int J Health Sci (Qassim)* 2008; **2(2)**: 3-7.
10 Teaching, learning, assessment, curriculum and pedagogy-https://www.sun.ac.za/english/learning-teaching/ctl/t-l-resources/curriculum-t-l assessment/ (accessed Dec 19, 2018).
11 Adhikari A, Bhattacharya S, Indu R, Ray M, Waghmare L — Perception of medical teachers towards undergraduate medical theoretical assessment system in a medical college of West Bengal. *Int J Res Med Sci* 2017; **5(12)**: 5396-401.
12 Adkoli B, Sood R — Faculty development and medical education units in India: A survey. *Natl Med J India* 2009; **22(1)**: 28-32.
13 Ferris HN, Flynn DO — 2015. Assessment in Medical Education; What Are We Trying to Achieve? *International Journal of Higher Education* 2015; **4(2)**: 139-44
14 Mafinejad MK, Arabshahi SKS, Monajemi A, Jalili M, Soltani A, Rasouli J — Use of Multi-Response Format Test in the Assessment of Medical Students' Critical Thinking Ability. *J Clin Diagn Res* 2017; **11(9)**: LC10-LC13.
15 Donner RS, Bickley H — Problem-based learning in American medical education: an overview. *Bull Med Libr Assoc* 1993; **81(3)**: 294-8.
16 Patil SY, Gosavi M, Bannur HB, Ratnakar A — Blueprinting in assessment: A tool to increase the validity of undergraduate written examinations in pathology. *Int J Appl Basic Med Res* 2015; **5(Suppl 1)**: S76-9.

Original Article

A Study of Serum Magnesium and Serum Zinc Concentration In Type 2 Diabetes Mellitus Patients with and without Diabetic Nephropathy

Tapas Paul[1], Polok Das[2], Prithwiraj Bhattacharjee[3], Dwijen Das[4]

Background : The deficiency of important trace elements like Magnesium and Zinc in terms of their serum concentrations in Type 2 Diabetes Mellitus patients, commonly claimed to be a cause of diabetic nephropathy. So the measurement of these two important trace elements in diabetic patients and their replenishment in deficient state could be a possible deterrent to the progression of diabetic nephropathy.

Materials and Methods : This study was undertaken at Silchar Medical College and Hospital, Silchar, from June 2018 to May 2019. A total of 100 patients were taken and divided into two study groups after satisfying the inclusion and exclusion criteria. Then the patients in each group were subjected test for estimation of zinc and magnesium concentration in serum.

Results : Decrease in Zinc level was seen in all Type 2 diabetic patients, but the decrease was more in the group with diabetic nephropathy (62.96±25.48 µg/dl *versus* 106.06±27.94 µg/dl). Also decrease in magnesium was more significant in the group of patients with diabetic nephropathy (1.75±0.38 mg/dl *versus* 2.07±0.18 mg/dl).

Conclusion : From this study it is evident that diabetic nephropathy is associated with lower serum zinc and magnesium level. There is a scope to study the impact of its replenishment to prevent diabetic nephropathy.

[*J Indian Med Assoc* 2021; **119(1):** 52-55]

Key words **: Type 2 Diabetes Mellitus, Diabetic Nephropathy, Zinc, Magnesium.**

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of diabetes mellitus are caused by a complex interplay of genetics and environmental factors[1]. Chronic and progressive nature of the disorder, which is associated with obesity[2], hypertension[3], advancing age[4] and inadequate screening[5] leads to deposition of harmful substances in the vascular endothelium ultimately causing development of micro angiopathies or microvascular complications[6]. These complications include retinopathy, nephropathy and peripheral neuropathy, which produce early death and increased morbidity and health care costs[7]. Normally insulin action was reported to be potentiated by some trace elements as chromium (Cr), magnesium (Mg), vanadium (V), zinc (Zn), manganese (Mn), molybdenum (Mo) and selenium (Se). It has been suggested that hypomagnesaemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post receptor insulin signaling, and/or altered insulin-insulin receptor interaction[8] and it is a possible metabolic factor involved in the pathogenesis of diabetic micro and macro vascular complications[9,10]. Again several complications of diabetes may be related to increased intracellular oxidants and free radicals associated to decreases in intracellular Zn and Zn-dependent antioxidant enzymes[11] and it has been observed to effectively ameliorate diabetes-related complications in various animal models[12]. Zn is also an effective inducer of gene and protein expressions of Metallothionein, a potent antioxidant[13]

Editor's Comment :

- **Low serum magnesium and zinc concentration was found associated with diabetic nephropathy as compared to those without nephropathy.**
- **It gives us an insight, whether replacement of these micronutrients can prevent development of diabetic nephropathy.**

Materials and Methods

This case control study was undertaken at Silchar Medical College and Hospital, Silchar, from June 2018 to May, 2019. Here 50 cases are diagnosed type 2 diabetes mellitus patients with diabetic nephropathy (DN) compared with 50 controls after age and sex matched from the same population, suffering from type 2 diabetes mellitus without diabetic nephropathy (NDN). Subjects suffering from hepatic disease, congestive heart failure and those taking mineral supplementation were excluded. Informed consent was obtained from participants and protocol was approved

Department of Medicine, Silchar Medical College, Silchar 788014
[1]MBBS, Postgraduate Student
[2]MD (Gen Medicine), Associate Professor
[3]MD (Gen Medicine), FICP, Professor & Head
[4]MD (Gen Medicine) FACP(USA) FRCP(Glasg) FIACM, Associate Professor and Corresponding Author
Received on : 25/02/2020
Accepted on : 15/07/2020

by Institutional ethical committee. Serum Zn and magnesium were estimated by colorimetric method. Also spot urine sample was collected to estimate urinary albumin and creatinine. Albumin creatinine ratio used to assess diabetic nephropathy. Statistical analysis used student 't' test and p value less than 0.05 were consider significant. The patients and control data were collected in excel sheet and calculated using Graph pad instat 3 software.

Result

In patients without diabetic nephropathy (control), the mean serum magnesium and mean serum zinc concentration were 2.07±0.18mg/dl and 106.06± 27.94μg/dl, and in those with diabetic nephropathy (case), the mean serum magnesium and mean serum zinc concentration were 1.75±0.38mg/dl and 62.96± 25.48μg/dl respectively and the difference were highly significant (p<0.0001). It is observed that patients without diabetic nephropathy had higher levels of mean serum magnesium and serum zinc in comparison with patients with diabetic nephropathy (Tables 1 & 2).

The range for the levels of mean serum magnesium in patients without and with diabetic nephropathy was (1.6-2.4)mg/dl and (1-2.3)mg/dl with confidence interval of (2.02-2.12) and (1.64-1.86) respectively. The median in control and case group was 2.0mg/dl and 1.9 mg/ dl, and the standard error of mean was 0.025 and 0.054.

The range for the levels of mean serum zinc in patients without and with diabetic nephropathy was (45-150) μg/dl and (21-117)μg/dl with confidence intervals of (98.11-114.01) and (55.71-70.20) respectively. The median in control and case group was 106.0 μg/dl and 55 μg/dl and the standard error of mean was 3.95 and 3.6 respectively (Table 3).

On comparing the two groups, the mean serum magnesium concentration in patients with diabetic nephropathy was observed to be lower by 0.32 than that in patients without diabetic nephropathy. This difference was highly significant (p<0.001). Similarly, the mean serum zinc concentration in patients with diabetic nephropathy was lower by 43.1 than that in patients without nephropathy. This difference was highly significant (p<0.001) (Table 4).

Table 1 — *Serum Magnesium and Serum Zinc Concentrations in Patients with and without Diabetic Nephropathy*

Group	Patients with NDN (Control)	Patients with DN (Case)	P-value
Mean Serum Magnesium Concentration (mg/dl)	2.07±0.18	1.75±0.38	<0.0001
Mean Serum Zinc Concentration (μg/dl)	106.06±27.94	62.96±25.48	<0.0001

The mean serum magnesium and serum zinc in patients without diabetic nephropathy were 2.096±0.17mg/dl and 107.51±29.58 μg/dl in patients aged 50 years or less, and 2.034±0.19 mg/dl and 103.58±25.18 μg/dl in patients above 50 years respectively. The differences between means were not significant. The mean serum magnesium and serum zinc in patients who had diabetic nephropathy were 1.65±0.48 mg/dl and 74.42±23.84 μg/dl in patients aged 50 years or less, and 1.77±0.37mg/dl and 61.09±25.51 μg/dl in patients above 50 years. The differences between means were not significant (Table 5).

The mean serum magnesium levels in female and male patients with and without diabetic nephropathy were1.8±0.40 mg/dl, 2.07±0.19mg/dl and 1.71± 0.36mg/dl, 2.08±0.17 mg/dl respectively. The differences were not significant.

The mean serum zinc levels in female and male patients with and without diabetic nephropathy were 64.26±25.70 μg/dl, 104.39±30.21 μg/dl and 61.85±25.73 μg/dl, c108.18±25.28 μg/dl. The differences were not significant.

Discussion

In this study, it has been observed that in patients without diabetic nephropathy, the mean serum magnesium concentration was found to be 2.07±0.18 mg/dl, and in those with diabetic nephropathy, the mean serum magnesium concentration was found to be 1.75±0.38 mg/dl.The difference was found to be highly significant (p<0.0001).

Das N *et al*[14] in their study found that the mean serum magnesium level in normal ACR and in the high ACR subjects were 2.416 ± 0.14 mg/dl and 1.646 ±

Table 2 — *Analysis of Serum Magnesium and Serum Zinc Levels of Sample Under Study*

Group	Number of Patients	Median		Min		Max		95%Confidence Interval		Standard error of Mean	
		Mg (mg/dl)	Zn (μg/dl)	Mg (mg/dl)	Zn (μg/dl)	Mg (mg/dl)	Zn (μg/dl)	Mg (mg/dl)	Zn (μg/dl)	Mg (mg/dl)	Zn (μg/dl)
Patients with NDN (control)	50	2.0	106	1.6	45	2.4	150	2.02-2.12	98.11-114.01	0.025	3.95
Patients With DN (case)	50	1.9	55	1	21	2.3	117	1.64-1.86	55.71-70.20	0.054	3.6

Table 3 — *Comparison of Serum Magnesium and Zinc Level between Patients without Diabetic Nephropathy and Patients with Diabetic Nephropathy*

Mean Serum Magnesium and Serum Zinc in the Different Sub-groups of Patients	Mean Difference	P Value
Without Diabetic Nephropathy (Control) — Diabetic Nephropathy (Case)	2.07-1.75=0.32	p<0.001
Without Diabetic Nephropathy (Control) — Diabetic Nephropathy (Case)	106.06-62.96=43.1	p<0.001

Table 4 — *Analysis of Serum Magnesium and Zinc with Regard to Age*

Groups	Mean Serum Magnesium (Mg/dl) ±SD and Mean Serum Zinc (µg/dl) ± SD				P-value	
	Age 50 years or less		Age >50 years			
	Mg	Zn	Mg	Zn	Mg	Zn
Patients with NDN (Control)	2.096 ± 0.17	107.51±29.58	2.034 ± 0.19	103.58± 25.18	>0.24	>0.20
Patients with DN (Case)	1.65 ± 0.48	74.42± 23.84	1.77±0.37	61.09±25.51	>0.46	>0.64

Table 5 — *Serum Magnesium and Serum Zinc Among Female and Male Diabetic Patients with and without Diabetic Nephropathy*

Groups	Mean Serum Magnesium (Mg/dl) ± SD and Mean Serum Zinc (µg/dl) ± SD				P-value	
	Females		Males			
	Mg	Zn	Mg	Zn	Mg	Zn
Patients without DN (Control)	2.07±0.19	104.39±30.21	2.08±0.17	108.18±25.25	>0.85	>0.63
Patients with DN (Case)	1.8±0.40	64.26±25.70	1.71±0.36	61.85±25.73	>0.44	>0.74

0.030 mg/dl respectively and was statistically significant with p-value <0.05.

Kishan R H *et al*[15] found mean serum magnesium levels among Type 2 DM with renal dysfunction, Type 2 DM without renal dysfunction and healthy controls were 0.795±0.199mg/dl, 1.319±0.103mg/dl and 2.33±0.28mg/dl respectively but the type of renal dysfunction did not mention in the study.

The finding of the present series was in agreement with the findings of the workers stated above, and may suggest a correlation between magnesium deficiency and development of microvascular complications in diabetes but we did not find any association between serum magnesium with age and sex.

Also in the present study, the patients without nephropathy, the mean serum zinc concentration was found to be 106.06±27.94 µg/dl, and in those with nephropathy the mean serum zinc concentration was found to be 62.96±25.48 µg/dl. The difference was found to be highly significant (p<0.0001).

In a study done by Jyothirmayi B *et al*[16], the serum levels of zinc was low in uncontrolled diabetes patients with micro-vascular complications and found to be (50±12.5, 95 ±20.42) (p< 0.001) when compared to control.

Mosaad A Abou-seif and Abd-Allah Youssef[17] found plasma zinc to be significantly less in diabetic patients with microvascular complications as compared to healthy controls. In Punjab, Puri M *et al*[18]), found zinc levels to be more decreased in the group with microangiopathic complications than in the group with uncomplicated diabetes mellitus (81.16+24.34 versus 92.01+20.17; p<0.05) and also Al-Timimi DJ, *et al*[19] found that advancing diabetic nephropathy represented by decreasing GFR and increasing micro albuminuria is associated with lower serum zinc levels.

In this study, the finding was in agreement with the findings of the workers stated above, and may suggest a correlation between Zinc deficiency and development of micro vascular complications in diabetes but we did not find any association between serum Zinc with age and sex.

Conclusion

The study showed that serum magnesium and serum zinc concentrations were lower in patients with diabetic nephropathy than in patients without diabetic nephropathy. So to elucidate the cause of this alternation, a large scale clinical trials are needed in order to determine whether the alterations in serum level of magnesium and zinc are cause or consequence of diabetes mellitus and correction magnesium and zinc deficiency could be effective to reduce the incidence of diabetic nephropathy and to further elucidate the association between serum magnesium and serum zinc with diabetic nephropathy.

Limitations :

(1) Single center study.
(2) Small sample size.
(3) Short duration of study.

Funding : None.
Conflict of Interest : None.
Ethical permission : Taken.

References

1 Powers AC — Diabetes mellitus. In Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo. Harrison's Principles of Internal Medicine.: McGraw Hill (Medical); 2018. 2850-59.
2 Hendrick AL, Jacqueline MD, Annette CM, Nejpels G, Robert JH — Blood pressure, lipids and obesity are associated with retinopathy. *Diabetes Care* 2002; **25 (8):** 1320-5.
3 United Kingdom Prospective Diabetic Study group — Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. *BMJ* 1998; **317:** 703-13.
4 Belmin J, Valensi P — Diabetic neuropathy in elderly patients. What can be done? *Drug Aging* 1996; **8(6):** 416-29.
5 Akbar DH, Mushtaq MA, Alagamdi AA — Inadequqte screening for microvascular complications among diabetic patients. *Diabetes International* 2001; **11 (1):** 22-4
6 King G, Brown LM — The cellular and molecular mechanisms of diabetic complications. *Endocrinological Metabolic Clinic North America* 1996; **25:** 255-70
7 American Diabetes Association — Economic consequences of diabetes mellitus in US in 1997. *Diabetes Care* 1998; **21:** 296-309.
8 Geiger H, Wanner C — Magnesium in disease. *Clin Kidney J* 2012; **5:** i25-38.
9 Mather HM, Levin GE. Magnesium status in diabetes. *Lancet* 1979 April 28; **1(8122):** 924.
10 Seelig MS, Heggtevit — Magnesium interrelationship in ischemic heart disease. *Am J Clin Nutr* 1974; **27:** 59-70.
11 Powell SR — The antioxidant properties of zinc. *Journal of Nutrition* 2000; **130:** 1447S-54S.
12 Adachi Y, Yoshida J, Kodera Y, *et al* — Oral administration of a zinc complex improves type 2 diabetes and metabolic syndromes. *Biochemical and Biophysical Research Communications* 2006; **351(1):**165-70.
13 Alscher DM, Braun N, Biegger D, *et al* —Induction of metallothionein in proximal tubular cells by zinc and its potential as an endogenous antioxidant. *Kidney and Blood Pressure Research* 2005; **28(3):** 127-33.
14 Das N, Mandal D, Ray Chaudhuri A, Karmakar A, Chandra Ray A, Mukhopadhyay M — Importance of Assessment of Serum Magnesium in type II Diabetes Mellitus Patients and its Relationship with Urinary MicroalbuminCreatinine Ratio. *J Med Res Prac*; **7(3):** 68-70.
15 Kishan Reddy H, Venugopal B — Association of serum Magnesium levels with renal function in patients with diabetes mellitus type 2. A cross sectional study in rural population of North Telangana.perspective in medical research September December 2018; **6(3):** 37-9.
16 Jyothirmayi B, Vasantha M — Study of Zinc and GlycatedHb Levels in Diabetic Complications. IJPCR, September-October. 2015; **7(5):** 360-3.
17 Mosaad A Abou-Seif, Abd-Allah Youssef — Evaluation of some biochemical changes in diabetic patients. Clinica Chimica Acta; 16 August 2004; **346(2):** 161-70.
18 Puri M, Uma Gujral SB — Nayyar.comparative study of serum zinc, magnesium and copper levels among patients of type 2 diabetes mellitus with and without microangiopathic complications. Innovative Journal of Medical and Health Science, 6 November – December 2013; **3:** 274-8.
19 Dhia J al-Timimi, Dhia M Sulieman, KaJeen R huSSen — Zinc Status in Type 2 Diabetic Patients: *Relation to the Progression of Diabetic Nephropathy.Journal of Clinical and Diagnostic Research* 2014; **8(11):** 4-6.

Original Article

Factors affecting High-Risk exposure amongst Health Care Workers (HCW): Audit of COVID-19 Risk Assessment Committee from Tertiary Care Centre in North East India

Vikas Kantilal Jagtap[1], Tony Ete[2], Lanalyn Thangkhiew[3], Evarisalin Marbaniang[4], Anita Marak[5], Daunipaia Slong[6], Dathiadiam Tongper[7], Nari Mary Lyngdoh[8], Amitav Sarma[9], Noor Topno[10]

Introduction: Quarantine and testing of High-Risk exposures of COVID-19 positive Health Care Worker (HCW) are recommended as per Ministry of Health & Family Welfare (MoHFW) guidelines. Many factors prevail when a HCW becomes High-Risk contact of a positive HCW during or after work hours.

Materials & Methods: Risk Assessment Committee (RAC) was constituted to assess the risk (high or Low) of exposure for contacts of COVID-19 positive HCW or patient. Direct or telephonic interview of HCW done for risk assessment. Based on the questionnaire of MoHFW guidelines, the contact is categorised as "High" or "Low" risk exposure. We performed an audit of these interviews to determine the various factors that lead to HCW being categorised as High-Risk contact of positive HCW.

Results: Having food together (lunch, tea, snacks etc.) was the commonest factor amongst the HCWs for reporting them as High-Risk contact. Other reasons included long conversations (>15minutes) without wearing a mask or proper PPE, sharing common vehicle to commute, personal visits to colleague's home, spending social time together and not wearing gloves or improper hand hygiene. Routine hospital services were severely affected (including shutting down of OPD & diagnostic services and delay in routine surgery) due to quarantine of High-Risk HCWs.

Conclusion: HCWs shortage and disturbance in routine hospital services is preventable by adequate social distancing norms and PPE protocols during and after work. Maintenance of social distancing among HCWs especially after work should be an important and ongoing task to counter COVID -19 transmission.

[*J Indian Med Assoc* 2021; **119(1):** 56-9]

Key words **: COVID-19, High-Risk Exposure, Health Care Worker, ICMR, MoHFW.**

From January 2020, many Health Care Workers (HCWs) are exposed to COVID-19 outbreak in India. HCWs (including doctors, nurses, sanitation, and administrative staff) are part of the hospital, which cater to COVID-19 positive patients and are theoretically at more risk to be infected compared to the general population. Similarly, if an HCW becomes positive for COVID-19 infection all his/her contacts are at risk of getting the infection. Exposure risk assessment from a positive HCW or patients (to his/her colleagues) is performed as per the Ministry of Health & Family Welfare (MoHFW) guidelines[1]. A quarantine period of 14 days and ICMR (Indian Council of Medical Research) testing protocol is advised for High-Risk category contacts of an HCW[1,2]. Low-Risk exposure contacts can continue normal work with advice to self-monitor their health for the development of symptoms and report if any such symptom occurs.

Some of the HCWs including doctors, nurses and supporting staff (technicians, cleaners. etc) have

Editor's Comment :

- **Health care workers (HCW) may become high risk contacts of COVID positive colleagues in the presymptomatic or asymptomatic stages.**
- **Social interactions greater than 15 minutes, sharing of beverages and snacks and vehicle sharing without proper distancing and masks are common ways of exposure**
- **HCW shortage and hampering of hospital services is preventable if caution is exercised.**

North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences, Shillong 793018

[1]MBBS, MD, DM, Associate Professor, Department of Radiation Oncology, Corresponding Author

[2]MBBS, MD, DM, Assistant Professor, Department of Cardiology

[3]MBBS, MS, Assistant Professor, Department of Ophthalmology

[4]MBBS, MD, Assistant Professor, Department of Pathology

[5]MBBS, MD, Assistant Professor, Department of Dermatology and Venereology

[6]MBBS, MD, Assistant Professor, Department of Forensic Medicine and Toxicology

[7]MBBS, MS, Assistant Professor, Department of General Surgery

[8]MBBS, MD, Associate Professor, Department of Anesthesia

[9]MBBS, MD, Associate Professor, Department of Anatomy

[10]MBBS, MS, Professor and Head, Department of General Surgery

Received on : 10/10/2020
Accepted on : 10/01/2021

designated duty in handling the COVID positive patients. These HCWs are provided with adequate Personal Protective Equipment (PPE) as per the MoHFW guidelines[3]. Rational use of PPE (full or Partial) is followed at our hospital for COVID and non-COVID areas as per these advisory orders. As the number of cases increased slowly at our hospital, some of the HCWs (including doctors, nursing officer, security officer and cleaning staff etc) were infected with Novel Corona Virus. The herculean task of contact tracing and risk assessment was done for the HCWs who encountered positive HCW. Risk Assessment Committee (RAC) attributed many factors to the designation of HCW as High-Risk exposure.

Materials and Methods

A Risk Assessment Committee (RAC) was formed to assess exposure level "High or Low" for the contacts of COVID-19 positive HCW or patient at our hospital. Contact Tracing Committee (CTC) derived the list of all possible contacts of a COVID positive HCW or patients. Designation of High Risk or Low-Risk Contact was done as per questionnaire form of MoHFW advisory guidelines [1]. RAC members did a direct interview (if the HCW is present in hospital) or telephonic interview of the HCWs. Whenever there was a doubt RAC committee members consulted amongst each other and nodal officer at our hospital to assign final risk category. RAC members and HCWs maintained social distancing norms and PPE protocols during these interviews. During the interview, the RAC committee noted many factors, which lead to the designation of High-Risk category for any HCW. We did an internal audit of all these factors to know the various reasons behind such situations. The RAC committee analyzed the interview data and recollected various factors in ranking orders that lead to High-Risk categorization of HCWs due to interaction with COVID positive HCW.

Results

Between 24 June 2020 and 30 July 2020, RAC members interviewed 409 HCWs (including Doctors, Staff, sanitation worker etc) Out of these 171 HCWs were categorised as High Risk and 238 as Low-Risk exposure. Out of this High-Risk Contacts 145 were exclusively from COVID-19 positive HCW (i.e. from the interaction of COVID positive HCW with other HCWs). On analysis of interview details of these High-Risk contacts of HCW, we found that having food together (lunch, tea, snacks etc.) was the commonest cause amongst the HCW for categorising them as High-Risk contact of positive HCW. Other reasons (in decreasing order) included long conversations (>15minutes) without wearing a mask or proper PPE, sharing common vehicle to commute. Personal visits to colleague's home, spending social time together and not wearing gloves or proper hand hygiene during or after work. Routine hospital services were severely affected (including shutting down of OPD & diagnostic services and delay in routine surgery) due to quarantine of most of the staff who were High-Risk exposure. Routine patient care was affected due to inadequate staff during this time.

Discussion

Human nature is to socialize and keep healthy social interaction. Social distancing is a non-pharmaceutical, most effective and simple way of prevention of COVID-19 transmission in public as well as hospital premises. Health Care Workers (HCW's) theoretically are at increased risk of COVID-19 infection owing to the service they provide in hospital for patients (COVID positive or negative). The MoHFW has put an advisory for Personal Protective Equipment (PPE) protocol for hospitals[3]. Despite these appropriate PPE measures, there is COVID-19 transmission amongst HCWs during their work. Many factors like a breach in PPE, the emergency aerosol-generating procedure (intubation, tracheostomy etc.), poor infection control, lack of PPE, improper donning and doffing of PPE etc. has been postulated to increase this risk of transmission[4,5]. Some authors also gave solutions for HCWs to limit infection spread [6,7]. Occasionally an HCW is an asymptomatic carrier of COVID-19 and they continue to work at the hospital. COVID-19 testing of such HCW is done when they are symptomatic or as a part of routine screening after completion of COVID duty as per ICMR protocol [2]. However, before an HCW is tested positive he has already interacted with other HCW at workplace either during his duty hours or after duty hours. Some of the HCW also hold other administrative posts (like the head of departments, members of various hospital committee, nursing in-charge etc etc) and carry out these responsibly over and above the clinical work at the hospital.

A contact is a person with a history of exposure with probable or confirmed case within 2-14 days [6]. Contact tracing of HCW who had come in contact with

COVID -19 positive HCW is a major issue. This contact could have happened either during the clinical or administrative work or sometimes as a personal interaction amongst HCW. Some of the HCW may have tea. Coffee, snacks after work, some may share a common vehicle to go home, some may visit each other's house with personal reasons or may go to market place together after work. There are many possibilities where one HCW can come in close contact with other HCW during or after work hours. Even though strict PPE protocols are maintained during clinical work (COVID duty, ICU, OPD, Non-COVID hospital areas, lab work etc.), such strict PPE protocols are not possible after work hours and as per advisory partial PPE protocols are maintained.

We observed that most of the time the personal contacts between COVID positive and negative HCW occurred outside duty areas where full PPE protocols are not necessary as per the advisory of MoHFW. The RAC members unanimously found that having tea, snacks, and food together is the commonest reason for close contact with positive HCW with obvious violation of PPE protocol. Long conversation of >15 minutes with fellow HCW after duty without face shields, sharing common vehicle to commute, visit (unofficial) to colleagues home, spending social time together in quarantine, not wearing gloves or not maintaining proper hand hygiene during personal interactions were other common reasons of close contact with positive HCW. Some awkward findings like giving each other haircut, donning and doffing together in changing room, having food together during the quarantine were noted during an interaction between RAC members and HCWs. Interaction of HCW in COVID duty with an HCW at non-COVID duty after work hours is also a factor noted in some cases. Sometimes HCW in COVID duty also went for official or administrative work to other non-COVID areas of hospital and interacted with other HCWs at non-COVID areas.

Our routine hospital services were severely affected (including shutting down of some OPD services & diagnostic services and delay in routine surgery) due to huge task of contact tracing and quarantine of High-Risk HCWs leading to the workforce shortage in some sections of the hospital.

Based on our interviews, discussions and risk assessment work analysis we came out with a take home message cum advisory to avoid or minimize the risk of transmission amongst HCW. This advisory must be followed in addition to the MoHFW guidelines, which are freely available online and are updated regularly.

Advisory /Take Home Message for Health Care Worker (HCW) :

(A) During work :

(1) Strict Social Distancing during work hours.

(2) Follow strict PPE protocol (COVID and non-COVID areas) as per advisory from hospital administration.

(3) Only one HCW allowed at any time inside changing rooms.

(4) Donning and Doffing of PPE must be done in designated areas. If the "Buddy system" is followed, only one HCW of a team should do donning and doffing at one time [1].

(5) HCW workers must not engage in common activities like tea, snacks, lunch etc.

(6) HCW should refrain from long interactions with fellow HCW and if required use of non-direct communication modes like mobile phones, intercoms or emails should be done.

(7) HCW working in COVID area should minimise/ avoid visits to Non-COVID areas of the hospital.

(8) HCW working in COVID areas should avoid interactions with HCW from non-COVID areas.

(9) HCW should avoid sharing common articles like pens, stationery material etc.

(B) After work :

(1) HCW should avoid social interaction with other HCWs after work hours.

(2) HCWs should avoid sharing tea, coffee and snacks after work hours.

(3) HCWs should avoid visits to each other's house unless essential.

(4) HCWs should avoid sharing vehicle to travel.

(5) For common buses for HCWs, maintain social distancing and PPE protocol.

(6) Maintain social distancing after work hours and especially during quarantine of HCWs.

There are some limitations to our analysis. The risk assessment form by the MoHFW does not have any column for noting reason for High-Risk exposure. RAC members analysed the factors as per recall from the interview. We have also not included the most common factor of High-Risk exposure i.e HCWs performing clinical/administrative work for long hours

or days together as per duty shifts. However, the point of this analysis is to determine other preventable factors. Strict adherence to social distancing, awareness of personal protection, use of appropriate PPE, adequate advisory, surveillance and proper actions would continue to play an important role in minimising the risk of COVID-19 infection among healthcare workers.

Conclusion

Maintenance of strict social distancing especially after work hours should be an important and ongoing measure to minimize further risk of transmission among HCWs. HCW shortage and disturbance in routine hospital services is preventable by adhering to social distancing norms, PPE protocols and appropriate advisory during and after work.

Financial Support & Sponsorship : NIL
Conflicts of interest : NIL
Source(s) of support : NIL
Presentation at a meeting : NIL
Conflicting Interest : NONE
Acknowledgement: NIL

References

1 Ministry of Health & Family Welfare advisory for health care worker. https://www.mohfw.gov.in/pdf/updatedAdvisoryformanagingHealthcareworkersworkinginCOVIDandNonCOVIDareasofthehospital.pdf
2 Indian Council of Medical Research testing protocol — https://www.mohfw.gov.in/pdf/ICMRrevisedtestingstrategyforCOVID.pdf
3 Ministry of Health & Family Welfare Guidelines for PPE — https://www.mohfw.gov.in/pdf/GuidelinesonrationaluseofPersonal ProtectiveEquipment.pdf
4 Mhango M, Dzobo M, Chitungo I, Dzinamarira T — COVID-19 Risk Factors Among Health Workers: A Rapid Review. Safety and Health at Work 2020; **6:**1-4.
5 Wang J, Zhou M, Liu F. Reasons for healthcare workers becoming infected with novel coronavirus disease 2019 (COVID-19) in China. *Journal of Hospital Infection* 2020; **105:**100-1.
6 Itodo GE, Enitan SS, Oyekale AO, Agunsoye CJ, Asukwo UF, Enitan CB. COVID-19 among Healthcare Workers: Risk of Exposure, Impacts and Biosafety Measures – A Review. *Int J Health, Safety and Environ* 2020; **6:** 534-48
7 Interim Operational Considerations for Public Health Management of Healthcare Workers Exposed to or with Suspected or Confirmed COVID-19: non-U.S. Healthcare Settings. Center for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/public-health-management-hcw-exposed.html , https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/public-health-management-hcw-exposed.html

Special Correspondence

[We are publishing this Special Correspondence to commemotare "WORLD LEPROSY ERADICATION DAY" on 30th January or Sunday Close to it]

World Leprosy Day : Looking Beyond MDT

Bani Prasad Chattopadhyay[1]

"Eliminating leprosy is the only work I have not been able to complete in my lifetime."

— Mahatma Gandhi

My knowledge about leprosy began in my late 20s when in 1999, I joined Gouripur Leprosy Hospital, Bankura, West Bengal as a Medical Officer in my early service life. Back then when media and the so called educated society had a belief that leprosy has declined or no longer exists, I was awed to see a 550 bedded hospital spreading across 200 acres of land (the largest leprosy hospital of Asia) actively running with patients even in waitlist. It's my confession that I've learnt about lepra reactions, complications like foot drop, ptosis etc from the caregivers, who were termed as "ex-patients"- a new salutation which I hadn't heard in relation to any other diseases. It's a burning example that even after cure, the stigma or taboo persists for lifetime . Most of the patients completed treatment settled in surrounding hospital making new village and colony due to non acceptance from family / community – same picture was persistent across the globe.

Thus to understand this social dimension, the basics of leprosy is discussed in brief.

Hansen's disease (named after Norwegian physician Gerhard Armauer Hansen) popularly known as leprosy is a chronic granulomatous and infectious disease caused by *Mycobacterium leprae*. It causes severe damage to peripheral nerve trunk [1] and to the skin which leads to deformity, impairment of function, disability and psychological disturbances, physical, mental & economical dependence and ultimately dehabilitation to destitution for developing stigma [2] . So early effective action is necessary for prevention deformities which are mild and reversible to begin with but becomes severe and permanent only later on [3].

Transmission of leprosy is poorly understood, although it is thought to be through inhalation of droplets containing the causative agent, Mycobacterium leprae (M. leprae). However, transmission via skin contact or other means cannot be entirely excluded. Leprosy has a reservoir in armadillos and a few other animals.

Up to 95% of patients exposed to M. leprae will not develop the disease, suggesting that host immunity plays an important role in disease progression and control.

The incubation time is variable, ranging from 2 to 20 years, or longer.[4]

With introduction of Multi Drug Therapy (MDT), prevalence rate has come down significantly worldwide. In India the rate has dropped from 57.8/10,000 in 1983 to 0.66/10,000 in 2016 after achieving elimination (PR < 1/10,000) at national level in 2005 [5]

India continues to account for 60% of new cases reported globally and is among the 22 "global priority countries" that contribute to 95% of world numbers of leprosy. New cases detection rate were 137,685 in 2007 and nine years later in 2016, the number remained almost the same at 135,485; a significant increase over the 127,336 cases was detected in 2015. The Grade II Disability (visible deformity as per WHO classification) rate in new case detected, which was rising till 2014-15(4.61%) was arrested in 2015-16(4.609) and though reverted in 2016-17(3.87%) indicates that the cases are being detected late in the community and there may be several cases which are lying undetected or hidden [6].Apart from initially detected new cases with grade 2 deformity (G2D), fresh G2D also occurs during or even after completion of MDT due to nurities and lepra reactions [7].Now there are more than 2 million of cases in India with G2D numbering approx 500,000 [8] 25% of leprosy patients have some degree of disability [9]

WHO launched the 5-year 'Global Leprosy Strategy 2016-2020' in April, 2016 titled 'accelerating towards a leprosy free world', with an aim to reduce the burden of leprosy by 2020 by not only reducing the case detection rate but also by reducing the number of new cases presenting with disabilities (less than one per Million) through early detection and by improving the

[1]Medical Officer, West Bengal Health Service, Department of Heath & Family Welfare, Govt of West Bengal, E-mail - bpcacademic@gmail.com

management of acute and chronic complications due to leprosy reactions, promoting self care support activities, rehabilitation and reconstructive surgery [1].

How is leprosy diagnosed? [4]

Normally, the diagnosis of leprosy rests on finding ***any one of three cardinal signs***:

- A definite loss of sensation in one or more pale (hypo pigmented) or reddish skin patches;
- One or more thickened or enlarged peripheral nerves with a loss of sensation and/or weakness in the muscles supplied by the nerve; or
- The presence of acid-fast bacilli in a slit skin smear. (though it is a less sensitive test)

The diagnosis of leprosy is often complicated by the fact that the way it presents depends on the type and strength of the body's immune response to *M. leprae* and largely based on clinical findings. No serological tests like HIV or SARS-COVID which can give instant results or to diagnose leprosy infection (latent leprosy) among asymptomatic contacts is available.

Immune response and classification :

Based on immune response of the patient towards the bacilli, Leprosy can be broadly classified as- (Ridley-Jopling Classification)

1. Tuberculoid, having relatively few bacteria in skin and nerves; characterized by a few flat or slightly raised skin lesions of various sizes that are typically pale or slightly red, dry, hairless, and numb to touch (anesthetic)

2. Lepromatous, having widespread disease and large numbers of bacteria, characterized by much more generalized disease, diffuse involvement of the skin, thickening of many peripheral nerves, and at times involvement of other organs, such as eyes, nose, testicles, and bone

3. Borderline, is an intermediate between tuberculoid and lepromatous type

There are subdivisional types too, like- Borderline Lepromatous Leprosy, Borderline Tuberculoid Leprosy, Indeterminate Leprosy.

In 1982, WHO proposed a simplified classification for effective public health control program, that has only two classifications

1. Paucibacillary (PB)- Patients with 1 to 5 skin lesions, without demonstrated presence of bacilli in a skin smear,

2. Multibacillary (MB)- Patients with more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions [4].

Lepra reactions- Lepra reactions are inflammatory reactions occurring in leprosy, due to circulating immune complexes, vasculitis, or T-cell reaction which may be induced by treatment.

1. Type 1 lepra reaction is a delayed type of hypersensitivity to *M. leprae* antigens, is also known as ***REVERSAL REACTION***, because the immune response initially appears to be declining and then "reverses" to become more intense. It may be a presenting feature of leprosy or may occur during treatment with MDT or even for three or four years after treatment has been completed (Rose, 1991). Starting treatment with MDT often appears to precipitate a Type 1 reaction, perhaps because the rapid killing of bacilli. It reflects a strengthening of specific cellular immunity against *M. leprae* towards the tuberculoid type.

2. Type **2 lepra reaction** is characterized by an acute immune complex vasculitis affecting the skin and other organs. It is also called ***erythema nodosum leprosum*** **(ENL).** It may be acute, recurrent or chronic and presents as a systemic illness, with high fever, systemic upset and prostration. Peripheral edema and transient proteinuria can also occur. Iritis and episcleritis, neuritis, nerve abscess, orchitis, lymphadenopathy, organomegaly, joint involvement, bone tenderness, especially over the tibia, are well recognized features of ENL.

If timely medical/surgical intervention is not done, lepra reactions can lead to organ damage resulting disability and even death.

Treatment :

Management of leprosy has evolved through different methods of management and drugs like *Chaulmoogra oil* to Dapsone immunotherapy, until universal MDT regime was proposed and implemented internationally in 1982 apart from isolation of the affected person.

MDT is followed as the standard treatment regimen as proposed by WHO GDG 2018-

Earlier it was 2 drug therapy for PB.

Usually patients are declared **RFT** (released from treatment) after completion of specific dose (smear or other laboratory investigation is not mandatory). Since 1995 WHO has provided MDT free of cost. Free MDT was initially funded by The Nippon Foundation, and since 2000 it is donated through an agreement with Novartis until at least 2020.

MDT is provided in blister packs, each containing 4 weeks' treatment. Specific blister packs are available for MB and PB leprosy, with different doses for adults and children.

Management of lepra reaction is done with appropriate dose of steroid, Thalidomide and necessary

Age group	Drug	Dosage and frequency	Duration	
			MB	PB
Adult	Rifampicin	600 mg once a month	12 months	6 months
	Clofazimine	300 mg once a month and 50 mg daily		
	Dapsone	100 mg daily		
Children (10–14 years)	Rifampicin	450 mg once a month	12 months	6 months
	Clofazimine	150 mg once a month, 50 mg on alternate days		
	Dapsone	50 mg daily		
Children <10 years old or <40 kg	Rifampicin	10 mg/kg once month	12 months	6 months
	Clofazimine	100 mg once a month, 50 mg twice weekly		
	Dapsone	2 mg/kg daily		

systemic managements.

Rehabilitation and disability prevention :

Nerve damage in leprosy causes physical impairments, mostly in eyes, hands and feet. Along with physical impairments, socio-economic conditions also stand as a barrier. The challenge in rehabilitation is to lessen or even reverse the bodily impairment, activity limitation and participation restriction that result from leprosy, so that the person can live as normal a life as possible. Rehabilitation focuses on the functioning of the individual rather than the disease, so leprosy rehabilitation programmer need to be multi-faceted. They may involve corrective surgery, physiotherapy and occupational therapy, and assistive devices. But they are also likely to involve aspects of individual empowerment – enabling people to manage self-care, develop new livelihoods, and other adaptations – and community education and advocacy that work towards enabling people to again participate fully in society. (*https://ilepfederation.org/about-leprosy/#prevention*)

- *Self care-* People with nerve damage need to examine feet and hands daily, checking for cracks, wounds, calluses and swollen areas, and have a daily routine of soaking the feet, scraping off dry skin, and applying oil. If ulcers develop, then resting and protecting the wound are essential to avoid further damage. Many patients find it helpful to join self-care groups. The right footwear can greatly reduce the risk of foot damage.
- *Physical rehabilitation*- Physical rehabilitation seeks to help people affected by the muscle weakness or physical damage caused by leprosy, in the normal activities of daily life. Physiotherapy exercises, occupational therapy, use of assistive devices, also sometimes accompanied by special training, are important to protect the weak muscles or anesthetized body parts. Surgery can correct some damaging consequences including paralysis and clawing of hands, foot drop and lagophthalmos (paralysis of lid preventing eyes from closing). Patients suffering from neuritis and foot ulcers benefit from splints and special footwear designed to assist in healing.
- *Socio-economic rehabilitation-* Many people affected by leprosy face the loss of their livelihoods as a result of prolonged hospitalization or the loss of physical capacity or the ongoing risk of damage to hands and feet. Socio-economic rehabilitation seeks to help people affected by leprosy to rebuild their lives through vocational training, micro-finance and business creation schemes, provision or improvement of appropriate housing, and advocacy at various levels to ensure that persons affected by leprosy and their family members are fully included in society.
- *Community-based rehabilitation*- community-based rehabilitation has been introduced for rehabilitation, equalization of opportunities, poverty reduction, and social inclusion. The essence of CBR is the 'twin-track' approach: mainstreaming (including people with disabilities, including leprosy, in mainstream community development as much as possible) plus disability-specific services and care where they are needed. CBR therefore includes factors like gaining or regaining a livelihood and becoming fully included in the life of the community.

Government, NGO, *policy makers plays a pivotal role here.*

Global leprosy situation :

The latest update from the WHO titled "Global leprosy update, 2016: accelerating reduction of disease burden: states that – although there has been a significant reduction in prevalence of the disease worldwide since the mid-1980s to elimination levels, new cases continue to arise indicating continued transmission[10] The registered global prevalence rate at the end of 2016 was 0.23 per 10,000 population, based on reports filed by 143 countries from different regions of the world.

To effectively manage the prevalent problems of

delay in diagnosis, discrimination etc, the Global strategy of 2016-2020 is built around three pillars-

(i) to strengthen government ownership, coordination, and partnership;

(ii) to stop leprosy and its complications; and

(iii) To stop discrimination and promote inclusion.

There is a special focus on women and children, strengthening referral systems, more effective contact tracing, assessing the value of chemoprophylaxis, and monitoring drug resistance [9].20th international leprosy Congress held at Manila Philippines September 2019 with the theme "Global Partnership in Addressing Current Challenges"promised to fulfill globally the slogan of Zero Transmission, Zero Disability and Zero Stigma and Discrimination.

We are eagerly waiting to host 21st international leprosy Congress at India

Targets of the Global Leprosy Strategy :

- Zero disabilities among new pediatric patients.
- A grade-2 disability rate of less than 1 case per 1 million people.
- Zero countries with legislation allowing discrimination on basis of leprosy.

Current strategies for leprosy treatment and prevention in India :

In India, the National Leprosy Eradication Programme (NLEP) is the centrally sponsored health scheme of the Ministry of Health and Family Welfare, Government of India; it is formulated centrally and implemented by state and Union Territories. After the implementation of MDT, India by the end of March 2011–2012 succeeded in achieving elimination at the state level in 34 states/UTs out of the total of 36 states/ UTs, in addition to achieving the national elimination target by the end of 2005. MDT treatments are highly effective- it cures 98% of patients with leprosy infection, relapse rate is very low and there are few reports of multi-drug resistance.

Vertical leprosy control program has been integrated to general health programs from sub center level.

The NLEP in its recent evaluation have acknowledged four alarming trends –

1. Presence of pockets of high endemicity,

2. Presence of hidden cases in the community,

3. The new case detection rate has remained almost the same since 2005,

4. Rising disability rates in new cases due to a delay in diagnosis.

The reasons for delay in diagnosis and treatment are[12] –

1. Medical (painless and insidious initial symptoms),

2. Cognitive (lack of awareness, inadequate knowledge about treatment availability, ignorance, lack of motivation),

3. Socio economic (work constraints, reluctance to lose daily wages due to hospital visits),

4. Psychological due to (stigmas and denial)

To address these challenges, NLEP advocated a three-pronged approach-

(a) "leprosy case detection campaign (LCDC)" in highly endemic districts;

(b) focused leprosy awareness campaign using ASHA and multipurpose health workers in "Hot Spots," where new cases with Grade 2 Disability (G2D) are detected; and

(c) area-specific plans for case detection in hard to reach areas.

It was felt that the major cause of hidden cases is low voluntary reporting in the community due to a lack of awareness as well as the continuing fear, stigma, and discrimination against leprosy. The **SPARSH Leprosy Awareness Campaign (SLAC)** was launched on 30th January 2017 and is a program intended to promote awareness and address the issues of stigma and discrimination[13]

Contact management is now considered an essential component of effective programme. For this, NLEP has undertaken various prevention strategies, like:

- *Chemoprophylaxis of contacts-* Leprosy Post Exposure Prophylaxis (LPEP) was launched globally in the year 2014 with an aim to evaluate the feasibility and efficiency of contact tracing and the provision of preventative treatment for leprosy under routine conditions in several countries and to determine the impact this has on leprosy incidence[14]The program has three prime components – contact tracing, screening and single-dose rifampicin (**SDR**) administration. Once a new patient has been diagnosed, health services actively screen household members and neighbors of the patient and examine them. Symptomatic persons are promptly referred for MDT and asymptomatic "contact persons" are offered a post-exposure prophylaxis (single-dose rifampicin) to reduce their risk of developing leprosy by 50–60%. It is designed to complement and be integrated into the NLEP rather than operating vertically[15]. Contact of leprosy for this programme is defined as someone who has had prolonged regular or interrupted contact with an index case during the last 1 year. A single dose of 600 mg of rifampicin is advocated as LPEP to household contacts above 35 kg body weight, 450 mg to individuals of 20 to 35 kg weight, and for those with

<20 kg body weight, 10–15 mg/kg of rifampicin as single dose.

• *MiP Immuno-Prophylactic Vaccine-* NLEP has introduced the *Mycobacterium Indicus Prani* (MiP) vaccine in a project mode in India from the year 2016. MIP vaccine has been shown to have both immunotherapeutic and immune-prophylactic effects in multibacillary leprosy patients and their contacts in both hospital and population-based trials. It also reduced the bacillary load, upgraded the lesions histopathologically, led to complete clearance of granuloma, reduced reactions, and neuritis and reduced the duration of MDT in leprosy patients[11]

• Nikusth, a web-based reporting system for leprosy- *For the ease of reporting and data management of registered leprosy cases, NLEP has launched "Nikusth," a web-based reporting system in India.[16] In addition, "Nikushth" will be helpful in keeping track of all the activities being implemented under the NLEP. NLEP is also planning to develop online training software for leprosy workers[17]*

Discrimination faced by leprosy patients :

Since ancient times, leprosy has been linked to taboos and stigmas and the persons affected by leprosy have faced intense rejection, fear, shame and resultant exclusion. This takes a toll on their mental health. Social discrimination leads to isolation of leprosy patients and often their families; as a result they cannot freely access the social resources of sanitation, water, education, markets etc. Apart from this *Legal* discriminations -As of 2019, there are 132 laws across 23 countries including India in respect of marriage ,employment, education ,transport that discriminate leprosy patients. The laws have their origin in 19th centuries and needs amendments.

Females generally face more social problems than males; unmarried girls with leprosy are often considered burden by her own family. Affected mothers are denied rights and isolated from her children.

Areas of concern :

1) There is a misconception in general public as well as policy makers about 'eradication' and 'elimination',

2) Lack of trained healthcare personnel at grass root level, which are based on ASHA and ANM workers, as dedicated leprosy workers have been shifted elsewhere after integration,

3) No special fund for dedicated leprosy work,

4) It is also true that newer generation health workers including doctors lacks hands on training on leprosy. So diagnosis of leprosy, which is almost entirely dependent on clinical findings, is often missed. Delayed diagnosis initiates most of the future problems.

World Leprosy Day :

The French humanitarian Raoul Follereau selected the date for World Leprosy Day. He wanted to pay homage to the life of Mahatma Gandhi and his death on 30th January 1948.Gandhiji dedicated his life for leprosy patients. There's a well known picture of Gandhiji nursing a leprosy patient- respected scholar Parchure Sastri; Gandhiji arranged his stay at Ashram in Sevagram, along with other residents. Gandhiji thus showed the path of care and rehabilitation simultaneously almost a century back. Let us pledge to fulfill Gandhi's dream-

References

1 WHO, global Leprosy Strategy,2016-2020. Operation manual
2 Meima A, Richardus JH, Habbema JD —Trends in leprosy case detection worldwide since 1985, *Lepr Rev* 2004 Mar; **75(1):** 19-33
3 Srinivasan H — Prevention of disabilities in patients with leprosy A PRACTICAL GUIDE
4 Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017
5 NLEP Annual Report 2015-2016. Central Leprosy Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, Nirman Bhavan, New Delhi
6 National Leprosy Eradication Programme, Guidelines for Sparsh Leprosy Awareness Campaign 2017: 4
7 Richardus JH, Nicholls PG, Croft RP, Withington SG, Smith WC — Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. *Int J Epidemiol* 200**4; 33(2):** 337-43
8 Richardus JH — Leprosy remains an important public health challenge in India. Indian J Med Res [serial online] 2013 [cited 2021 Jan 11]; 137: 878-9.
9 Singhi M K Ghiya B C, Gupta D, Kachhawa D — Disability rates in leprosy. *Indian J Dermatol Venereol Leprol* 2004; **70:** 314-**6**
10 Weekly Epidemiological Record No. 35. 2017 Sep 1;92:501–20.
11 Rao PN, Suneetha S — Current Situation of Leprosy in India and its Future Implications. *Indian Dermatol Online J* 2018; **9(2):** 83-89.
12 Samraj A, Kaki S and Rao PSS (2012). Help-Seeking habits of untreated leprosy patients reporting to a referral hospital in Uttar Pradesh, India. *Indian J Lepr* **84 :** 123-9.
13 NLEP Newsletter. 2017 Jan-Mar;II(1)
14 Novartis foundation. Leprosy post-exposure prophylaxis (LPEP) programme. [Last accessed on 2017 Nov 20
15 Tiwari A, Mieras L, Dhakal K, Arif M, Dandel S, Richardus JH. Introducing leprosy post-exposureprophylaxis into the health systems of India, Nepal and Indonesia: A case study. *BMC Health Serv Res* 2017; **17:** 684
16 NLEP Newsletter, Vol 1, Issue 2; April 2016
17 WHO Goodwill Ambassador's Newsletter No 80, June 2016. Available from: http://www.smhf. Or. Jp/ambassador/pdf/Nl080.pdf.

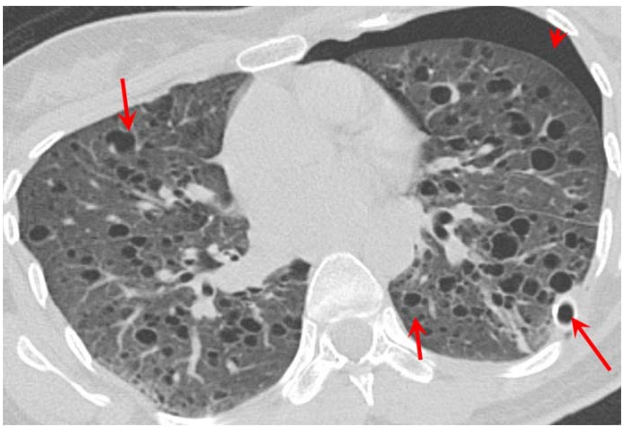
Image in Medicine

Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

Axial CT scan of chest of a 33-years old lady who presented with sudden shortness of breath.

Questions :
(1) What is the diagnosis ?
(2) What is Lymphangio-leiomyomatosis (LAM)?
(3) How to differentiate LAM from Langerhans cell histiocytosis (LCH)?



Answers :

(1) Lymphangio-leiomyomatosis (LAM). Thin-walled cysts (arrows) are seen randomly distributed in both the lungs. A small left pneumothorax (arrowhead) is seen. The long arrow shows the intercostal drainage tube.

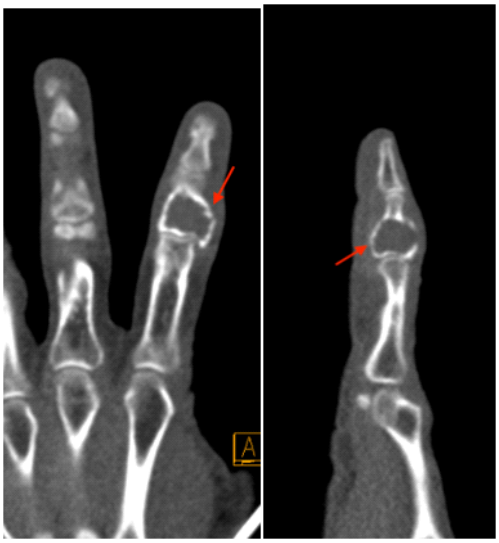
(2) LAM occurs in women in the child-bearing age group. Often the initial manifestation is pneumothorax. LAM is multi-organ disease characterized by infiltration of immature-appearing smooth muscle cells in the airways and along lymphatics. It occurs either as a pure pulmonary disease or in association with tuberous sclerosis. In some patients there may be associated findings including lymphangiomas.

(3) The distribution of cysts is the key distinguishing feature of LAM from LCH. In LAM, cysts may involve the juxtaphrenic recesses, unlike in LCH. The cysts in LAM tend to spare the extreme lung apices. The cysts in LAM are typically thin wall and round in shape. The diagnosis is usually confirmed without biopsy by measuring the serum VGEF levels, which are typically high.

Quiz 2

A 65 year old lady presented with swelling around middle phalanx of 2nd finger.

Questions:
(1) What is the diagnosis?
(2) What are the common locations of this lesion?
(3) Name the syndromes associated with multiple enchondromas.



Answers:

(1) Well defined osteolytic expansile lesion with narrow zone of transition is seen in middle phalanx of 2nd finger (arrow). These imaging findings favour diagnosis of enchondroma, which was confirmed on biopsy.

(2) Enchondromas are typically seen in central or eccentric location within the medullary cavity of tubular bones. It is commonly seen in small tubular bones of hands, feet and in large bones like femur, tibia and humerus.

(3) Syndromes associated with multiple enchondromas are: i)Ollier disease – it is non-hereditary, sporadic disorder characterised by multiple enchondromas located in the metaphyseal regions. ii) Maffucci syndrome – is a congenital non-hereditary dysplasia characterised by multiple enchondromas with soft-tissue venous malformations.

Picture This by Jankharia, Mumbai, Maharashtra
[1]MD, DNB (Radiology)
[2]MD, DMRD (Radiology)

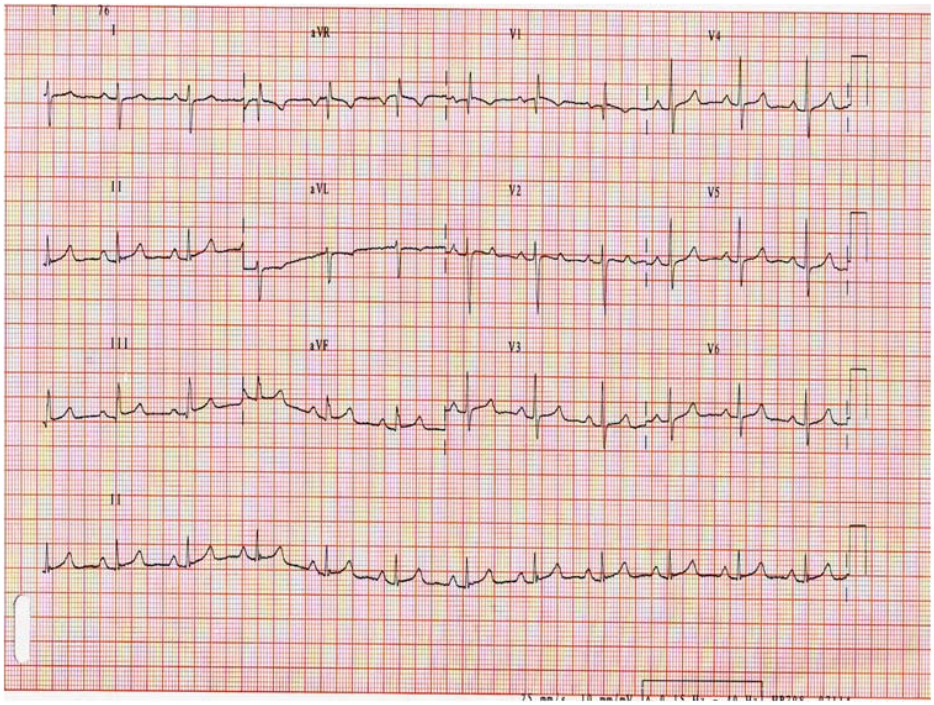
Student's Corner

Become a Sherlock Homes in ECG

M Chenniappan[1]

Series 1 :

ECG



"Thick, Thin, Thick"

(A Thin Fellow Between 2 Thick Fellows)

This is the ECG of 48-year-old male has heart disease since childhood.

1. **What are the ECG signs?**
2. **Why is this clue?**
3. **What is practical implication?**

ECG SIGNS :

The ECG shows sign of RVH and Right Axis Deviation (RAD). Since the patient has history of heart disease since childhood it is likely to be Adult Congenital heart disease like ASD,PS or Tetralogy of Fallot (TOF).

THE CLUE :

There is an important clue in this ECG,which indicates the diagnosis of TOF. The R wave in V1 is tall, and it suddenly drops in voltage in V2 and once again it picks up in lead V3. This is because in TOF, the RVH is peculiar. The right free wall hypertrophied, whereas the trabecular portion is thinned out. There is IVS hypertrophy. This is reflected in ECG as follows:

1. Tall R in V1 – RV free wall hypertrophy
2. Small R in V2 – Trabecular thinning
3. Tall R in V3 – IVS hypertrophy

Because of this, clue of thick (v1) , Thin (V2) , Thick (V3) is given.

THE PRACTICAL IMPLICATION :

The commonest cyanotic heart disease in adults is TOF. The peculiar ECG changes in an adult with central cyanosis makes the possibility of TOF as the diagnosis even without Echo.

[1]Adjunct Professor, Dr MGR Medical University, Tamilnadu; Senior consultant cardiologist, Tamilnadu; Ramakrishna Medical Centre, Apollo Speciality Hospital, Trichy

Case Report

Mesangioproliferative Glomerulonephritis in a case of Pulmonary Atresia with Ventricular Septal Defect (Pseudotruncus arteriosus) : An Interesting Case Report

Shubhanshu Pal[1], Pradip Kumar Datta[2], Adrija Ganguly[3], Sayan Saha[3], Himadri Roy[3]

Pulmonary atresia with ventricular septal defect (PA-VSD) with pulmonary arterial supply arising from aorta represented by large Major Aortopulmonary Collateral Arteries (MAPCAs) associated with a right sided aortic arch is an uncommon anomaly. Most of the patients succumb to severe respiratory compromise or congestive cardiac failure very early. Around 9% of adults with congenital heart disease likely to have moderate to severely impaired renal function and as a result have an additional adjusted 3 fold increased mortality risk. Here we are reporting a case with PA-VSD with glomerulonephritis, a rarely reported entity.

[*J Indian Med Assoc* 2021; **119(1):** 67-9]

***Key words*: Pseudotruncus arteriosus, Pulmonary Atresia, Ventricular Septal Defect, Mesangioproliferative Glomerulonephritis.**

Truncus Arteriosus is characterized by a single great artery with a single semilunar valve that leaves the base of the heart and gives rise to coronary, pulmonary and systemic circulations. In 1949, Collett and Edwards classified this anomaly into four types. Type IV ie, Biventricular aorta with an atretic pulmonary valve, is now considered as ultimate expression of severity in Fallot's tetralogy[1]. However considering the similarities with Truncus Arteriosus it is also sometimes called Pseudotruncus.

Cyanotic Nephropathy (CN) is often accompanied by congenital cyanotic heart diseases. Hyperviscocity due to polycythemia can be the underlying cause. In addition, failure of a compensatory mechanism to respond to reduced Renal Plasma Flow may be responsible[2].

We are presenting a case of 30 years old patient, with Pseudotruncus and Cyanotic Nephropathy.

Case Report

Our patient is a 30 year old, non diabetic, non hypertensive, non hypothyroid male patient who presented to us with facial puffiness and pedal swelling for two weeks duration. The swelling started from face and later involved his feet. It was associated with diminished urine output although no history of frothy or cola coloured urine was present. He had no history of preceding fever, sore throat, skin infection, joint pain or any drug intake. He also didn't complaint of any shortness of breath, cough, palpitation or jaundice. Although his past history was significant with bluish discolouration of body since 6th day of life and also there was history of recurrent chest infection (8-9 episodes each year since the age of 6 years). But there was no history suggestive of cyanotic spell. After admission on examination he was found to have ruddy conjunctiva, cyanosis, grade 3 clubbing and pedal oedema. His Jugular venous pressure (JVP) was engorged. His respiratory rate was 20/min, pulse rate was 90/min. He had no palpable neck gland. His Cardiovascular Examination findings were as follows: Apex was found to be in 6th intercostal space, outside midclavicular line with a palpable diastolic thrill. Grade 3 parasternal impulse and Epigastric pulsation was present. On Auscultation, S1 was soft, S2 soft, single, S3 was present. A grade 4 mid-diastolic murmur was heard at the apex, a grade 3 continuous murmur was heard over the lower left sternal area and a grade 3 early diastolic murmur was heard best in the neo-aortic area. ECG suggested Right axis deviation, tall peaked P waves and tall R waves in V1. Chest X-Ray (Fig 1) was done, which showed, marked

Editor's Comment :

- **Congenital Cyanotic Heart Diseases are systemic diseases that may present with symptoms even beyond cardiovascular system.**
- **Although rare, complex cyanotic congenital heart diseases can present very late.**
- **With well-developed MAPCAs, patient may have no symptoms from cardiovascular point of view.**
- **Cyanotic Nephropathy can be associated with long standing cyanotic heart disease.**
- **Management of these complex congenital heart diseases with their complications is still a matter of discussion.**

Department of General Medicine, IPGMER & SSKMH, Kolkata 700020
[1]MBBS, MD Trainee, Junior Resident and Corresponding Author
[2]MD (Medicine), Professor
[3]MBBS, MD Trainee, Junior Resident

Received on : 12/02/2020
Accepted on : 25/08/2020

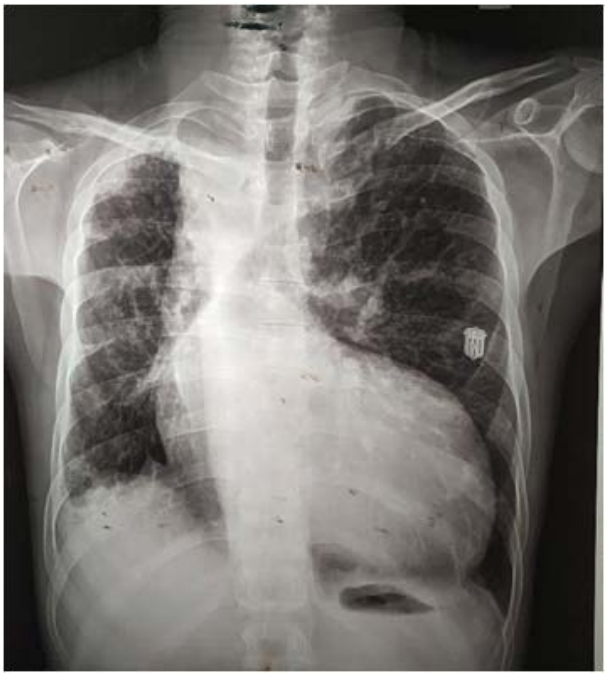


Fig 1 — Chest X Ray Showing Right lung hypoplasia and increased vascularity on Left Side. Cardiomegaly is present

Table showing the various blood parameters during hospital stay

Hb(gm/dl)	20.5
PCV(%)	63
TLC	9,100
Platelet	1.09L
Ur/Cr(mg/dl)	64/1.7
Na/K (m/mol)	136/4.4
Ca	7.6
ALP/ALT/AST	79/22/29
TB	0.8
TP/Alb	5.2/2.8
Chol/TG/HDL	281/266/65
C3/C4 (mg/dl)	111/35.2
dsDNA (IU/ml)	<10
PT/INR	13.8/0.97

dilatation of Pulmonary trunk and increased flow on the left lung, the Right lung seemed to be hypoplastic. Cardiomegaly was appreciated. We had a suspicion that we might be dealing with a case of Truncus Arteriosus, so we wanted to have a cardiological evaluation along with workup for renal parameters as the history was suggestive of renal pathology. Talking about his blood parameters, Haemoglobin and Haematocrit both were persistently raised, Creatinine was marginally elevated, deranged lipid profile with raised serum

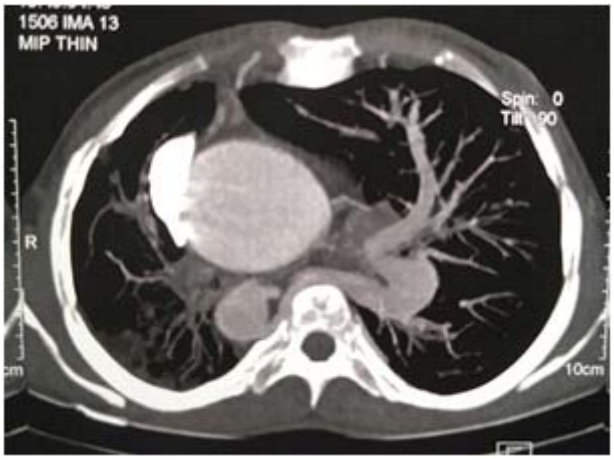


Fig 2 — Renal Biopsy showing (Upper left) Subcapsular Global Sclerosis, (Upper right) Glomerular hypercellularity, (Lower left) Tubular atrophy and Interstitial fibrosis, (Lower left) Similar changes in Silver methanamine stain

cholesterol and triglyceride. Urinalysis suggested albuminuria 2+, 24 hours quantification was done, which came out to be 2.7g. Renal biopsy was done which showed Mesangio-proliferative Glomerulonephritis with focal subcapsular scarring (Congenital heart disease associated glomerulopathy) (Fig 2). Regarding cardiological evaluation, 2D Echo with Colour Doppler suggested, moderate to severe

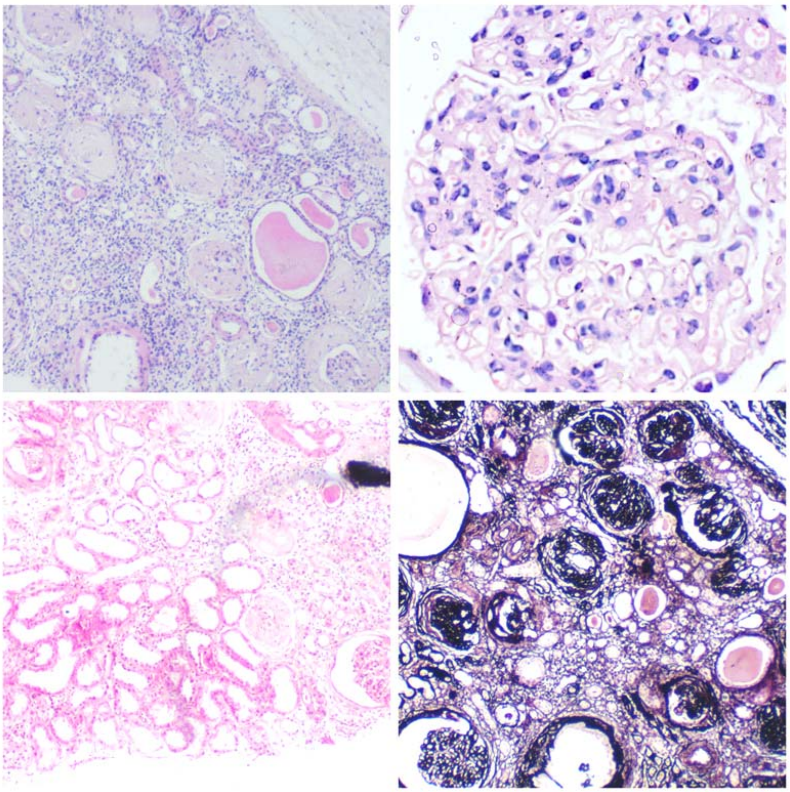


Fig 3 — CT Angiography showing that MAPCA going to Left Lung, whereas in Right lung vascularity is compromised

Augmented Reality, doubly committed aorta (<50%) with subaortic Ventricular Septal Defect (VSD) and Major aortopulmonary collateral arteries (MAPCA). Cardiac MRI was suggested, which suggested Truncus arteriosus and CT Cardio-Pulmonary Angiography (Fig 3) was done for confirmation. It showed, multiple non-confluent MAPCAs bilaterally with hypoplastic Right pulmonary artery, Right sided Aortic arch, large subaortic VSD (16 mm) with overriding of aorta. Pulmonary artery was not visualized. The features were suggestive of Pseudotruncus arteriosus.

After proper discussion with respective departments, it was concluded that neither there is any scope of surgical intervention, nor it is necessary. The patient was started on Renin Angiotensin Aldosterone System (RAAS) blocking agent for proteinuria and Statin for dyslipidemia and discharged for follow up.

Discussion

Pseudotruncus Arteriosus is indeed a very rare disease reported in the literature. In a study, 21 such cases were reviewed and the oldest survivor reported was 36 years old.[3] Thus for those survivors, treatment goals and management of complications are not well delineated. But congenital heart disease are systemic diseases with consequences reaching far beyond the heart. Cyanotic Nephropathy is one such complication. It is related to duration of cyanosis and extent to which the haematocrit is elevated.[4] In a study the renal changes observed were Glomerulomegaly, Glumerulosclerosis, Periglomerular fibrosis, Hyperplastic arteriosclerosis and Interstitial fibrosis.[5] Regarding management of nephropathy, a study using Enalapril for 12 months showed reduction in proteinuria in 80% of patients, although no change was demonstrated in Glomerular filtration rate (GFR), Renal plasma flow or Filtration fraction.[6] In this patient also, RAAS Blocker therapy has been initiated and the outcome needs to be evaluated during follow up.

References

1 Perloff Joseph K, Marelli Ariane J — Clinical recognition of Congenital Heart Disease. Elsevier. 2012.

2 Inatomi J, Matsuoka K, Fujimaru R, *et al* — Mechanisms of development and progression of cyanotic nephropathy. Pediatr Nephrol 21, 1440-1445 (2006).

3 Lafargue Robert T, *et al* — Pseudotruncus arteriosus, A review of 21 cases with observations on oldest reported case. 1967; **19(2):** 239-246

4 S Dittrich, NA Haas, C Buhrer, C Muller, I Dahnert, PE Lange — Renal impairment in patients with long-standing cyanotic congenital heart disease. 2007.

5 Prajakta A Gupte, Pradeep Vaideeswar, Bhuvaneshwari M Kandalkar — Cyanotic Nephropathy- A Morphometric Analysis. 2013.

6 Y Fujimoto, *et al* — Nephropathy of Cyanotic Congenital Heart Disease: Clinical Characteristics and Effectiveness of Angiotensin-Converting Enzyme Inhibitor. 2002.

1. "Nature Makes Penicillin; I just found it."

2. "One sometimes finds what one is not looking for. When I woke up just after dawn on Sept. 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I guess that was exactly what I did."

— Sir Alexander Flemming

Case Discussion in Medicine

Fever : A Case Based Approach for the Clinicians

Atanu Chandra[1], Uddalak Chakraborty[2]

Fever is the presenting manifestation of several infective, inflammatory or neoplastic disease conditions. Acute febrile illness (duration of fever <14 days) is mainly due to infective etiologies in our country. A thorough history including the contextual history and meticulous general examination along with systemic survey will guide the clinician to localize and identify the etiology, recognize the danger signs, streamline the investigations and initiate management early. Clinicians should use rapid diagnostic tests to exclude common tropical infections such as malaria and dengue. Early identification of sepsis is also very important to reduce mortality and morbidity. It is prudent to avoid injudicious administration of antibiotics, if the duration of fever is less than 3 days in absence of any danger sign, and initial negative rapid tests. The purpose of this article is to remind the clinicians about the clinical approach to a febrile patient in day to day practice.

[*J Indian Med Assoc* 2021; **119(1):** 70-5]

Key words **: Acute febrile illness; inflammation; malaria; dengue fever; scrub typhus; leptospirosis.**

Case 1 :

A 44-year-old gentleman from Bihar presented with history of fever, non-productive cough and dyspnea for the past 3 weeks. There were neither any past history of tuberculosis or contact, nor had any chronic diseases such as diabetes, hypertension or malignancy. He was immunocompetent and denied any intake of long term medicines. On examination he was febrile with an oral temperature of 100.8°F, tachycardia (heart rate of 116 beats/min), blood pressure of 112/74 mmHg, respiratory rate of 26 /min and oxygen saturation of 98% on room air. He had a body weight of 58 kg. There was no definite history of weight loss.

Further Course in Hospital, Outcome and Follow-up :

On careful examination, jugular venous pulse was found to be raised and pulsatile along with muffled heart sounds. Laboratory investigations revealed mildly raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Electrocardiography (ECG) revealed sinus tachycardia with low voltage complexes. Chest X-ray showed right sided basal consolidation with pleural effusion along with increased cardio-thoracic ratio. USG-guided thoracentesis was performed fluid for acid fast staining, and PCR test for M Tuberculosis was negative. Pericardiocentesis was performed by trans-thoracic echocardiography and 600 ml of straw-colored pericardial fluid was drained. PCR test for M. tuberculosis was found positive. The patient responded well to drainage of the pericardial fluid and dyspnea subsided. He was orally started on anti-tuberculosis drugs and steroids. The patient was responding well to the treatment, with no recurrence of symptoms or any signs of deterioration in 3-months follow-up.

Editor's Comment :

- **The most important step to evaluate a febrile patient is history taking and clinical examination.**
- **Clinicians should follow the stepwise approach in management of a febrile patient.**
- **Appropriate tests to identify common infective causes should be done when suspected.**
- **Investigations in a febrile patient should be focussed and the choice of antibiotics if needed be appropriate.**

Case 2 :

A 45-year old gentleman presented with pain involving knee, hip shoulder, wrist and small joints of the hands along with unresolved fever for two weeks. He also complained of severe sore throat for the same duration. There was non-pruritic macular rash over extremities and the trunk which resolved spontaneously after two days of its appearance. On examination, he was febrile (temperature of 101.4°F). There was synovitis of the aforementioned joints, throat was mildly congested; lymphadenopathy or organomegaly was absent and other systems were unremarkable.

Further Course in Hospital, Outcome and Follow-up :

He admitted to have two similar presentations with

Department of Internal Medicine, RG Kar Medical College and Hospital, Kolkata 700002

[1]MD (Internal Medicine), DNB (Internal Medicine), MRCP (UK), Assistant Professor and Corresponding Author

[2]MD (Internal Medicine); Senior Resident

Received on : 04/01/2021

Accepted on : 05/01/2021

six months gap over the past two years. He was diagnosed as rheumatoid arthritis and given methotrexate, but he stopped taking the medication after the pain subsided. Basic blood parameters showed leukocytosis of 21.1×10^9/L (88% neutrophils), elevated transaminases, very high CRP (244 mg/L), elevated ESR (96 mm/hr) and markedly elevated serum ferritin (14,400 ug/L). Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (Anti-CCP) and antinuclear antibody (ANA) were all negative. Renal and coagulation profiles were normal. Blood and urine cultures did not reveal any evidence of infection. Computed tomographic (CT) scan of the thorax and abdomen were normal. He was diagnosed to have adult onset Still disease (AOSD) using the Yamaguchi criteria. He was started on oral analgesics and steroid (prednisolone 30 mg/day). The symptoms gradually improved and methotrexate was added after normalization of liver enzymes. During follow up, steroids were tapered off gradually and the symptoms improved.

Introduction :

Fever is one of the cardinal symptoms of many infective, inflammatory or neoplastic diseases[1, 2]. There is much debate regarding the definition of acute febrile illness. In Indian context, most of the literature has defined the duration of less than two weeks[3, 4]. There is inter-individual and circadian variation in body temperature; moreover rise of normal body temperature is seen in various physiological conditions, such as women after ovulation, after heavy meals or exercise.[2] The generally accepted definition is oral temperature >98.9ºF (evening). Acute undifferentiated fever can be defined as fever of less than two weeks duration without any localizable or organ-specific clinical features.

History Taking in a Febrile Patient :

The most important step to evaluate a febrile patient is to take a thorough and meticulous history to explore problems of the patient from different perspectives such as, the chronology of symptoms, patient's perspective and review of each system to appropriately localize the source of the fever[5, 6].

■ **Symptom analysis for fever :**

To confirm the presence of fever (whether true or factitious fever); duration of febrile illness (acute or chronic); onset (abrupt or gradual); pattern (continuous or intermittent); severity- how it affects the activity of daily living; aggravating and relieving factors; treatment received before presentation and associated symptoms suggesting any systemic illness.

■ **Pattern of temperature changes :**

Continuous fever : Temperature remains above baseline throughout the day and fluctuation is less than 1 °C in 24 hours period, eg, lobar pneumonia, urinary tract infection, enteric fever.

Intermittent fever : Fever is present only for a certain period of the day, ie, temperature returns to the baseline in between episodes of fever

Following are its types- Quotidian fever (periodicity of 24 hours) classically seen in *Plasmodium falciparum* malaria; Tertian fever (periodicity of 48 hours) classically seen P. *vivax* or *P. ovale* malaria; Quartan fever (periodicity of 72 hours) classically seen in *P. malariae* malaria.

Remittent fever : Temperature remains elevated throughout the day and fluctuation is more than 1 °C in 24 hours, *seen in* infective endocarditis.

Pel-Ebstein fever : There is much debate in the existence of it. It is used to describe the specific pattern of fever seen in Hodgkin's lymphoma, where the temperature is high for one week and normalized in the next week and so on.

■ **Chills and rigors :**

Presence of chills accompanied by rigors is mainly seen in malaria, sepsis with abscess, cholangitis and pyelonephritis.

■ **Night sweats :**

Night sweats are characteristic of lymphoma and tuberculosis.

■ **Headache and Delirium :**

Fever from any aetiology may provoke headache. Severe headache and altered sensorium in a febrile patient ay point towards more ominous causes such as, meningitis and encephalitis.

■ **Muscle pain :**

Myalgia is seen in infections such as influenza, dengue fever, malaria, leptospirosis and scrub typhus.

■ **Respiratory tract symptoms :**

(1) Sneezing, sore throat, purulent nasal discharges are suggestive of upper respiratory tract infection.

(2) Pain over the sinus and headache suggests sinusitis

(3) Cough, sputum, respiratory distress or wheezing suggests a lower respiratory tract infection.

■ **Genitourinary symptoms :**

Symptoms such as frequency of micturition, burning sensation, loin pain suggests urinary tract infection. Associated vaginal or urethral discharge indicates sexually transmitted infection (STI) or pelvic inflammatory disease(PID).

■ **Abdominal symptoms :**

Presence of diarrhea, with or without blood in the stool, significant weight loss and pain abdomen point

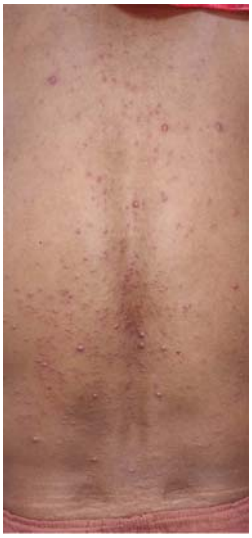


Fig 1 — Dew drops on rose petal appearance of Varicella

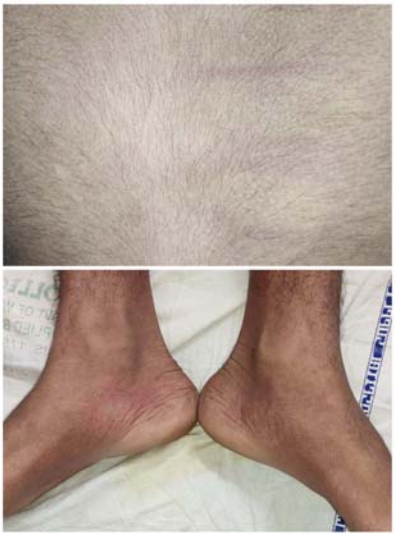


Fig 2 — Maculopapular blanching rash of dengue

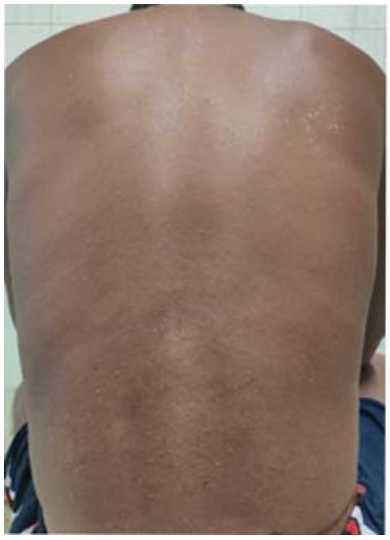


Fig 3 — Morbilliform rash of measles

Fig 4 — Eschar of Scrub typhus

towards gastroenteritis, intra-abdominal infective foci, abdominal tuberculosis, inflammatory bowel disease (IBD) or malignancy.

■ **Joint symptoms :**

Pattern of joint involvement and number of joints involved are very important for diagnostic purpose. Fleeting arthritis indicates rheumatic fever. Monoarthritis always need prompt evaluation to exclude serious etiologies such as septic arthritis or gouty arthritis. Asymmetric oligoarthritis is associated with reactive arthropathy. Symmetric polyarthritis is associated with collagen vascular diseases and infective causes such a dengue and chikungunya.

■ **Constitutional symptoms:**

Weakness, anorexia, weight loss, fatigue, night sweats

■ **Contextual History:**

(1) Any medical problems such as diabetes, asthma, heart disease, tuberculosis or jaundice.

(2) Past history of surgery, intervention or transfusion.

(3) Drug history (drug fever is common in penicillin, cephalosporin, sulphonamides, phenytoin and anti tuberculous agents), use of any herbal or alternative medicine and immunization history

(4) Personal and social history regarding addiction (smoking, alcohol, intravenous drug abuse), water supply and sanitation status, exposure to animals and birds, sexual history and dietary habits.

(5) Travel history and occupational history

Essential Clinical Examination in a Febrile Patient :

Meticulous clinical examination by a physician is of paramount importance to localize the possible etiology and streamline the essential investigations.[7]

■ **General Examination :**

General examination starts with assessment of higher mental functions. In acute febrile illness, presence of altered mental function is an ominous sign and may indicate etiologies such as meningitis or encephalitis. Presence of signs of meningeal irritation with or without focal neurological deficit needs immediate admission and evaluation, Drowsiness in a patient of malaria is an ominous sign. Fever with gross emaciation suggests chronic disorders such as tuberculosis, immunosupression or malignancy.

The other important points in general examination with their common associations are:

- **Pallor :** malaria, hematological malignancy
- **Clubbing :** lung abscess, empyema , infective endocarditis
- **Cyanosis :** severe pneumonia (particularly important in patients with COVID-19)
- **Jaundice :** viral hepatitis, cholangitis, Leptospirosis, Scrub typhus
- **Alteration in pulse rate** : Normally, there is rise of pulse rate of 8-10 beats/min with each degree Celsius rise in core body temperature. Relative bradycardia is seen in infective conditions such as enteric fever (Faget Sign) and Dengue; whereas relative tachycardia is seen in rheumatic fever and myocarditis.
- **Lymphadenopathy :** Presence of

pathologically enlarged lymph nodes point towards tuberculosis, infectious mononucleosis or lymphoproliferative disorders.

- **Alteration in blood pressure:** Severe hypotension in febrile patients may indicate septic shock or acute meningococcal septicemia with adrenal involvement
- **Tachypnea:** In this present Coronavirus Pandemic, pyrexia with tachypnea and cough should be thoroughly evaluated and properly treated.

■ **Systemic Survey:** Focused examination of the respiratory, cardiovascular, neurological, lymphoreticular and musculoskeletal systems to find out underlying etiology.

Fever with Rash[8] :

- **Distribution of rash**- Central (in infectious mononucleosis, measles, dengue and adult onset Still's disease); peripheral/acral (in Chikungunya, infective endocarditis and secondary syphilis).
- **Morphology of the rash**- maculopapular rash (in measles, drug rash, rubella and initial phase of dengue fever); vesiculobullous rash (in Varicella and disseminated Herpes simplex infection); purpuric rash/ necrotic rash (meningococcemia, later stages of dengue and thrombotic thrombocytopenic purpura); nodular rash (in erythema nodosum and Sweet syndrome); confluent desquamative rash (in Kawasaki disease and scarlet fever). **Eschar** is a necrotic lesion at the site of chigger bite with a central black crust which is surrounded by a zone of erythema. It is painless usually. Presence of eschar is a pathognomonic sign of scrub typhus.
- **Day after the onset of fever-** Though there are many exceptions to this rule, but it is a very useful guide in suspecting the aetiology of the exanthematous fever (Day 1-Varicella, Day 2- Scarlet fever, Day 3- Small pox, Day 4- Measles, Day 5- Typhus, Day 6- Dengue, Day 7- enteric fever)

■ The images of rashes in chickenpox, dengue, measles and the pathognomonic eschar have been included as Figs 1-4.

Fever with Generalized Lymphadenopathy :

Although the cervical group of lymph nodes are the most commonly afflicted nodes, but careful examination of all the other areas along with detailed evaluation of lymphoreticular system is of paramount importance to find out the underlying etiology. Lymph node size of >1 cm in cervical or axillary and >1.5 cm in inguinal; any tender or matted node and lymphadenopathy of any size in supraclavicular or epitrochlear region should be considered as significant.

Tuberculosis and lymphoma are the two most common causes of generalized lymphadenopathy in our country. Localized enlargement of lymph nodes is most likely due to local infection or malignancy. However, the detailed discussion on this topic is beyond capacity of this article.

Red-flag Signs in a Febrile Patient:

- Altered sensorium
- Hypothermia or hyperthermia
- Hypotension
- Bleeding manifestation
- Persistent vomiting
- Severe anemia
- Desaturation and cyanosis

Essential investigations in a febrile patient[9, 10, 11] :

The initial investigation in a febrile patient should be complete blood count with peripheral blood smear. Both leukocytosis and leukopenia may indicate serious infections or sepsis. Complicated malaria sometimes present with hemolysis and dengue fever often presents with hemoconcentration (raised packed cell volume) and thrombocytopenia. Hematological malignancies are often diagnosed incidentally on routine hemogram. A careful examination of peripheral smear often diagnoses causative organisms such as malaria and microfilaria.

Urine analysis is also comes under the initial investigations panel as asymptomatic urinary tract infections are not very uncommon especially in pregnancy and old age. Moreover, presence of active sediments indicates toward glomerular pathology.

Liver and renal function tests are also needed because those are affected in several infectious or inflammatory pathologies and the values are often necessary to predict the toxicities of the commonly administered drugs.

In the pediatric age group, most of the febrile illnesses are often caused by respiratory tract infections and those are often caused by viruses. In the recent pandemic scenario, it is very necessary to evaluate all patients with fever and respiratory symptoms, and order the tests for COVID-19 if clinically indicated.

Most of the acute febrile illnesses in our country are caused by infections. So, etiological diagnosis of them is very important for early initiation of proper treatment. The common rapid tests performed to rule out tropical infections and their confirmatory tests are summarized in Table 1.

It is a very rational practice to send blood culture in all patients with acute febrile illness before

administration of antibiotics. Septicemia must be ruled out initially in immunocompromised, post-surgical and post-transplant patients. HIV serology should be ordered in presence of atypical infections or typical infections in atypical fashion. Appropriate imaging such as CT scan, X-rays or ultrasonogram in a febrile patient should be considered according to the localizing features elicited from the history or clinical examination. Fever with altered sensorium should be considered as a medical emergency and an urgent CSF study with brain imaging should be done. Evaluation of the auto-immune/auto-inflammatory diseases should be done when there is strong clinical suspicion and the investigations do not suggest infectious etiology of the febrile illness.

Table 1 — *Common rapid tests performed to exclude the tropical infectious etiologies*

Common tropical infections	When to suspect	Rapid tests	Confirmatory tests
Malaria	High grade fever with chills and rigor; presence of haemolysis, hepatic or renal dysfunction when complicated.	Antigen test- may be done after fever onset. Sensitivity and specificity high (95%)	Microscopy by thick and thin smear
Enteric fever	Fever in presence of prominent gastrointestinal symptoms	IgM antibody- may be done at the end of first week Sensitivity-47-98%, Specificity- 58-100%	Blood culture
Scrub typhus	Fever with presence of eschar is pathognomonic; neurological, hepatic or renal involvement when complicated.	IgM antibody (ELISA)-may be done at the end of first week, Sensitivity- Variable Specificity- 90-100%	IFA or PCR
Dengue fever	Fever with headache, bodyache, retro-orbital pain, rash and thrombocytopenia; haemorrhage or shock when complicated.	NS1- day 1-5 IgM- day 5-onwards Sensitivity- 60-80% Specificity- 80-90%	PCR
Leptospirosis	Fever with myalgia, hepatic and renal dysfunction.	IgM- may be done after 8-10 days of onset Sensitivity-80% after 2nd week Specificity- Variable	PCR/Culture

Stepwise Management in a Patient of Acute Febrile Illness :

(1) To assess the severity of symptoms and early recognition of sepsis through detailed history, examination and focussed investigations

(2) Appropriate localization and identification of complications or danger signs

(3) Use of rapid diagnostic tests to exclude common tropical infections such as malaria and dengue

(4) Use of anti-pyretics alone, if duration <3 days, no danger sign, and initial rapid tests are negative

(5) Meticulous history taking, examinations and focussed investigations and management if fever persists for longer duration with initial negative rapid tests.

(6) Search for the uncommon aetiologies and specialist opinion in case of acute undifferentiated febrile illness with negative culture which persists despite the initial empiric antibiotics

References

1 Walter EJ, Hanna-Jumma S, Carraretto M, Forni L — The pathophysiological basis and consequences of fever. *Crit Care* 2016 Jul 14; **20(1):** 200. doi: 10.1186/s13054-016-1375-5. PMID: 27411542; PMCID: PMC4944485.

2 Mackowiak PA — Concepts of fever. *Arch Intern Med* 1998 Sep 28; **158(17):** 1870-81. doi: 10.1001/archinte.158.17.1870. PMID: 9759682.

3 Shelke YP, Deotale VS, Maraskolhe DL — Spectrum of infections in acute febrile illness in central India. *Indian J Med Microbiol* 2017; **35:** 480-4.

4 Morch K, Manoharan A, Chandy S, *et al* — Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. *BMC Infect Dis* 2017; **17:** 665

5 Whitby M — The febrile patient. *Aust Fam Physician* 1993 Oct; **22(10):** 1753-5, 1758-61. PMID: 8279999.

6 Bonadio WA — The history and physical assessments of the febrile infant. *Pediatr Clin North Am* 1998 Feb; **45(1):** 65-77. doi: 10.1016/s0031-3955(05)70583-6. PMID: 9491087.

7 Shann F — Diagnosing fever by touch: observational study. *BMJ* 1998; **317:** 321

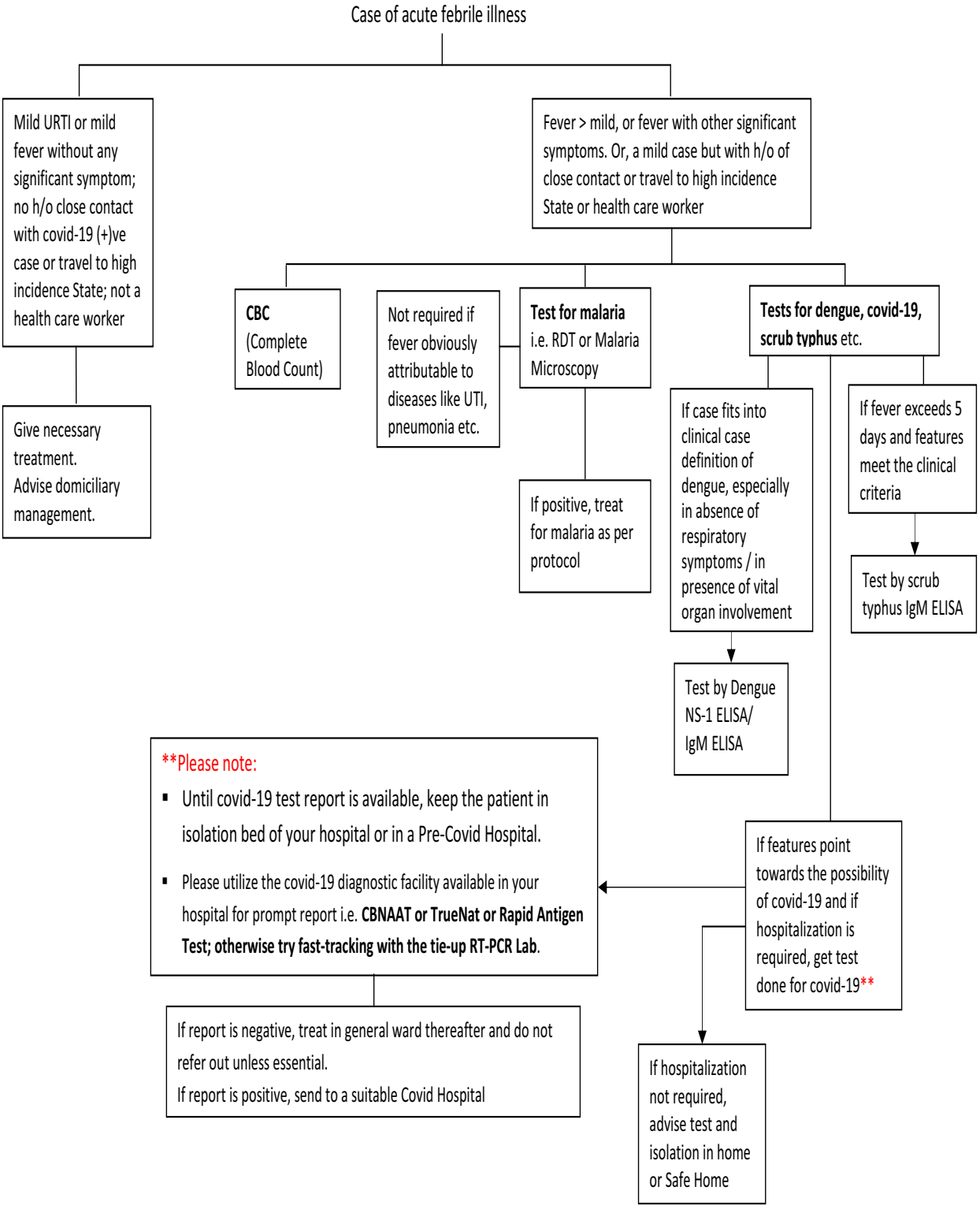
8 Vaidya SR, Kamble MB, Kumbhar NS — Laboratory-based investigation of fever with rash cases in the Maharashtra State - India, 2014 to 2017. *J Med Virol* 2019 Jun; **91(6):** 972-978. doi: 10.1002/jmv.25407. Epub 2019 Feb 5. PMID: 30680754.

9 Bhargava A, Ralph R, Chatterjee B, Bottieau E — Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions. *BMJ* 2018 Nov 29; **363:** k4766. doi: 10.1136/bmj.k4766. PMID: 30498133.

10 Wright WF, Auwaerter PG — Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma. *Open Forum Infect Dis* 2020 May 2; **7(5):** ofaa132. doi: 10.1093/ofid/ofaa132. PMID: 32462043; PMCID: PMC7237822.

11 Roth AR, Basello GM — Approach to the adult patient with fever of unknown origin. *Am Fam Physician* 2003 Dec 1; **68(11):** 2223-8. PMID: 14677667.

Attending a fever case in the OPD or ER, keeping covid-19 & dengue scenario in the mind



(Source : Department of Health & Family Welfare, Government of West Bengal)

Pictorial CME

Moya Moya Disease — A Rare Case of Stroke in Children

Sumi M Pillai[1], Jayakrishnan M P[1], Tanu Arora[1], K Malcolm Jayaraj[2], S Sakthivelayutham[2], P R Sowmini[2], M Sathish Kumar[2], R Viveka Saravanan[3], K Mugundhan[4]

A 13 year old boy admitted with weakness of right upper limb and lower limb and speech difficulty since 1day. Neurological examination showed right hemiparesis with power -MRC grade of 2/5 and 4/5 in right upper limb and right lower limb respectively. MRI Brain (Fig a) showed acute infarct in left post central gyrus, corona radiata, posterior limb of internal capsule and insular cortex. MR angiogram revealed complete occlusion of supraclinoid segment of left internal carotid artery (ICA) with multiple collaterals. CT angiogram (Fig b) revealed complete occlusion of left ICA with reformation of left anterior cerebral artery and middle cerebral artery. Digital substraction angiography (DSA) revealed narrowing of distal cavernous and supra clinoid segment of left ICA with multiple collaterals, flow of contrast into left posterior cerebral artery(PCA) via posterior communicating artery noted (fig c). Complete occlusion of M1 segment of left MCA with multiple adjacent collaterals noted. Right ICA and MCA were opacified and a diagnosis of moyamoya disease was made and patient was treated with antiplatelets and physiotherapy. Patient improved over a period of 4-6 weeks.

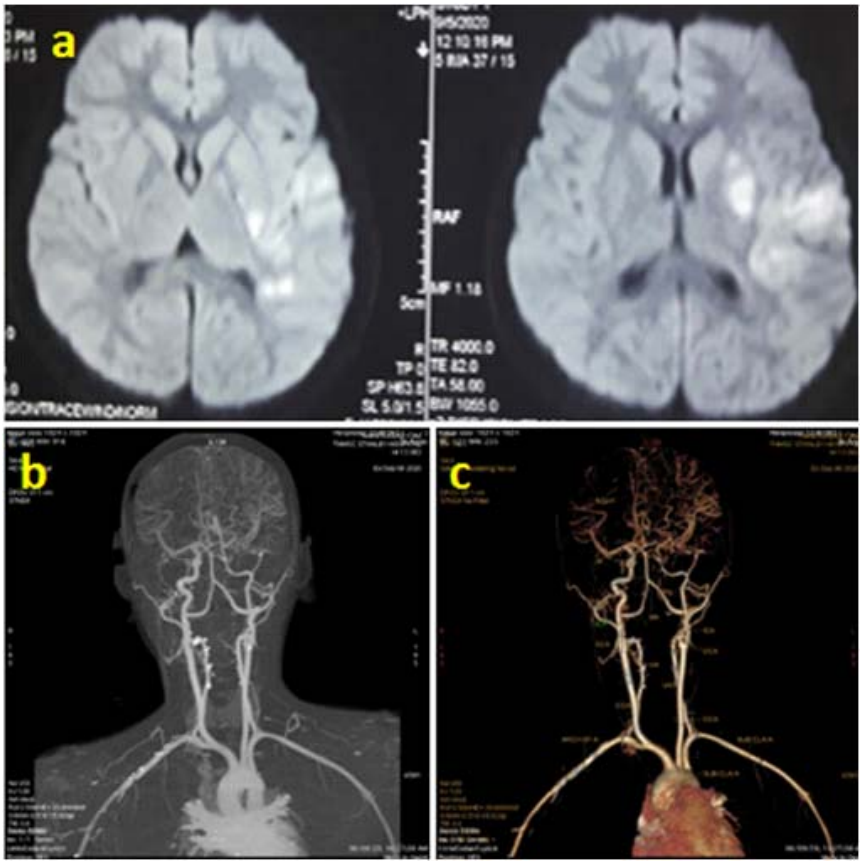


Fig 1 — (a) MRI DWI Image showing acute infarct in left post central gyrus,corona radiata, posterior limb of internal capsule and insular cortex; (b) CT angiogram Revealed complete occlusion of left ICA with reformation of left anterior cerebral artery and middle cerebral artery; (c) DSA revealed narrowing of distal left ICA with multiple collaterals and complete occlusion of left MCA. Right MCA and bilateral ACA and its branches were opacified

Discussion

Moyamoya disease (MMD) is a type of chronic occlusive cerebrovascular disease. Its major characteristic is a steno-occlusive change at the end of the internal carotid artery (ICA), middle cerebral artery (MCA) and/or proximal anterior cerebral artery (ACA), which is accompanied by the formation of smoke-like abnormal blood vessels in the base of the skull in digital subtraction angiography (DSA).

The clinical signs of MMD mainly include two types: Cerebral ischemia and cerebral hemorrhage. These two types of symptom differ in their distribution between pediatric and adult patients. Most of the pediatric patients present with progressive cerebral ischemia, including transient cerebral ischemic attacks and cerebral infarctions. Mental

Department of Neurology, Stanley Medical College, Chennai 600001
[1]DM, Postgraduate Student
[2]MD, DM, Assistant Professor
[3]MD, DM, Associate Professor
[4]MD, DM, FRCP (G,L&Ire) FACP, FICP, Professor and Head

decline or seizures may be the first symptom in children. In half of the cases in adults, intracranial hemorrhage is the first symptom.

In 1996, Japan issued a guideline[1] for the diagnosis and treatment of Moyamoya disease, MMD) which suggests the following manifestations on cerebral angiography (i) Stenosis or occlusion at the end of the carotid artery, the proximal ACA and/or MCA; (ii) an abnormal vascular network in the vicinity of stenotic occlusion lesions in the arterial phase; and iii) the above manifestations are bilateral.

In the 2012 guidelines[2], cerebral angiography remains the gold standard for the diagnosis of MMD with the staging performed according to angiographic findings. The system most widely used for its evaluation is the Suzuki staging system, in which the cerebral angiographic findings of MMD patients are divided into 6 stages based on the progression degree of smog-like blood vessels.

The current drug treatment for in MMD only targets its clinical symptoms, including ischemia and hemorrhage, by exerting anti-coagulant or hemostatic effects.

The preventive effect of surgical revascularization treatment has been clinically demonstrated on ischemic events[3]. However, intra- and extra-cranial revascularization for the prevention of recurrence of bleeding in patients with hemorrhagic MMD is controversial. Surgical revascularization of MMD includes 3 types: Direct revascularization, indirect revascularization and combined revascularization. In the direct revascularization surgery, the most common method is superficial temporal artery-MCA anastomosis.

MMD is an important cause of cerebral stroke in pediatric and adult patients. A definitive diagnosis of MMD must be made as soon as possible, so that with treatment relatively long-term prognosis can be achieved. Surgery remains an important treatment for MMD, but an individualized clinical treatment strategy should be selected according to the condition of each patient. This case report serves to emphasize the need for a high index of suspicion to diagnose this rare stroke.

References

1 Fukui M — Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis (moyamoya' disease). Research committee on spontaneous occlusion of the circle of Willis (moyamoya disease) of the ministry of health and welfare, Japan. *Clin Neurol Neurosurg* 1997; **99(Suppl 2):** S238–S240. doi: 10.1016/S0303-8467(97)00082-6.

2 Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis) Neurol Med Chir (Tokyo) 2012; 52: 245-66. doi: 10.2176/nmc.52.245.

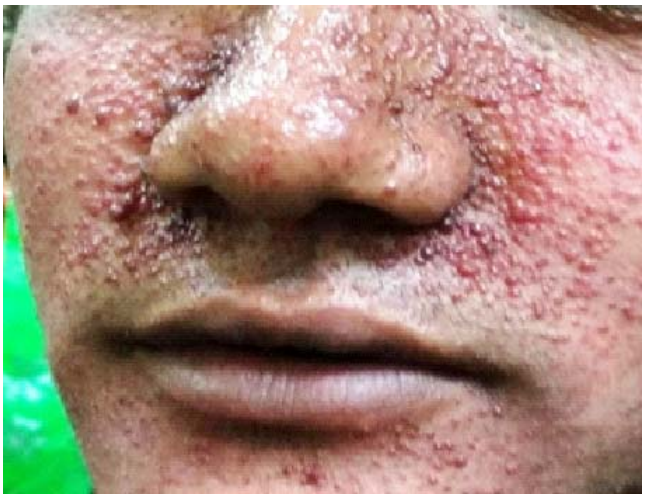
3 Fujimura M, Tominaga T — Lessons learned from moyamoya disease: Outcome of direct/indirect revascularization surgery for 150 affected hemispheres. *Neurol Med Chir (Tokyo)* 2012; 52: 327-332. doi: 10.2176/nmc.52.327.

Pictorial CME

A Cause of Recurrent Seizure — A Neuro Cutaneous Syndrome

Pranabananda Pal[1], Nandini Chatterjee[2]

A 14 year old male from a village of Purulia presented to Medicine OPD with history of recurrent seizure for last 1 year without any h/o fever or altered sensorium. His seizure was recurrent and according to the description of the eye witness it was generalized. He gained consciousness following the events and continued his daily work. His birth history was normal and no developmental delay was there. He had poor academic performance and could not continue his school after class 4. He also developed some behavioral abnormality like occasional agitation and compulsiveness. He had a low socio economic background and he took alternative medicines for his ailment. But the seizure activity persisted and he attended a tertiary hospital in Kolkata.



On examination he hadpapular skin lesions on his face which was present since his childhood, gradually increasing in number but they did not bother him as they were painless and non pruritic.

Based on typical skin lesion of facial angiofibromas (adenoma sebaceum) and h/o recurrent seizures , it was clinically suspected to be a case of TUBEROUS SCLEROSIS.

Q1. What are the other sites to examine?

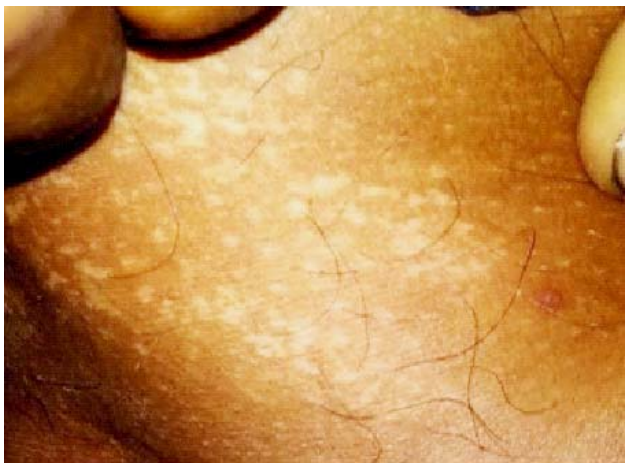
Q 2. What are the MRI features of Tuberous sclerosis?

MRI BRAIN

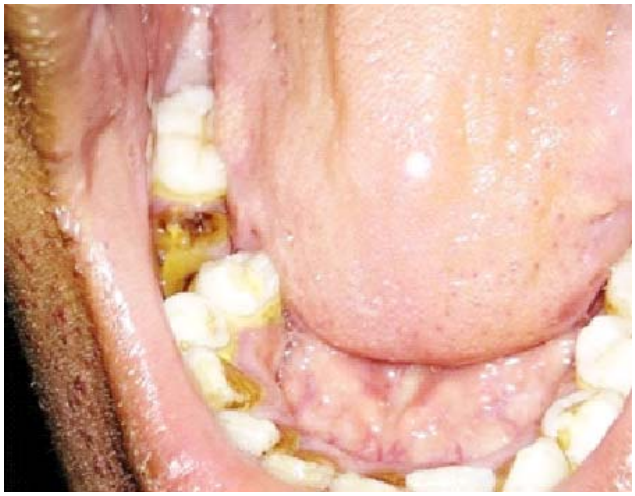
MRI brain reveals classical cortical tubers in both T1 and T2 weighted images.

Q3. What is the genetic basis of the syndrome?

It is an autosomal dominant disorder with an incidence of ~1 in5000–10,000 live births. It is caused by mutations in either the *TSC1*gene, which maps to chromosome 9q34 and encodes a protein termedhamartin, or the *TSC2* gene, which maps to chromosome 16p13.3and encodes the protein tuberin. Hamartin forms a complex withtuberin,

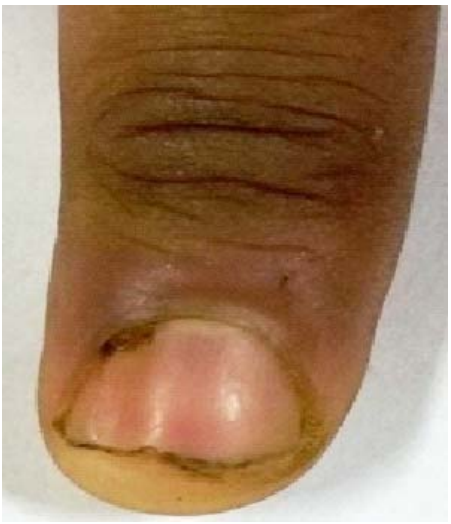


Generalised skin condition: Ash-leaf (Hypomelanic) macules in the back

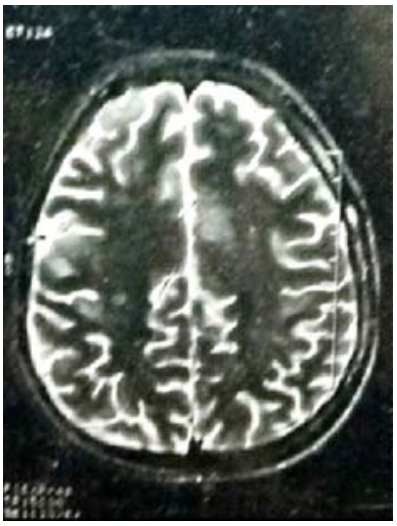


Dental lesions: Dental enamel pits

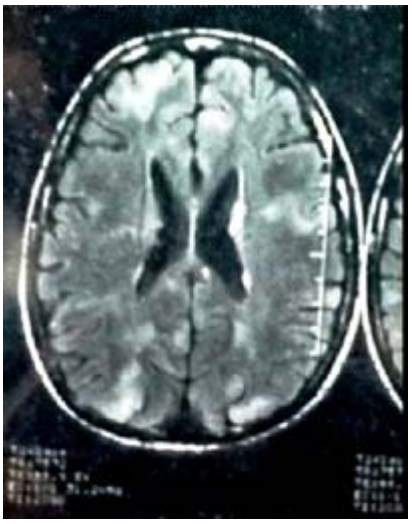
Department of Medicine, IPGMER & SSKM Hospital, Kolkata 700020
[1]MBBS, Postgradate Trainee
[2]MD, FICP, Professor and Corresponding Author



Nail condition : Periungual fibromas/ Koenen'stumors



T1W : Subependymal nodules: form in the walls of ventricles



T2W : cortical and subcortical tubers

which inhibits cellular signaling through mTOR, and acts asa negative regulator of the cell cycle.

Q4. What are the cutaneous lesions associated with this condition?

i. A**denoma sebaceum**becomes manifest usu-ally between 5 and 10 years of age and typically consists of reddened nodules on the face (cheeks, nasolabial folds, sides of the nose, and chin) and sometimes on the forehead and neck.

ii. Subun-gual fibromas,

iii. Shagreen patches (leathery plaques of sub-epidermal fibrosis, situated usually on the trunk)

iv. Leaf-shaped hypo-pigmented spots.

Q5. What are other associated conditions with Tuberous Sclerosis?

Patients with tuberous sclerosismay have seizures, mental retardation, periungualfibromas, renal angiomyolipomas, and benign cardiac rhabdomyomas. Thesepatients have an increased incidence of subependymal nodules, corticaltubers, and subependymal giant-cell astrocytomas (SEGAs).

6. What are the possible management modalities?

Patientsfrequently require anticonvulsants for seizures. SEGAs do not alwaysrequire therapeutic intervention, but the most effective therapy is withthe mTOR inhibitors sirolimus or Everolimus, which often decreaseseizures as well as SEGA size.

References

1 Cardis MA, DeKlotz C — Cutaneous manifestations of tuberous sclerosis complex and the paediatrician's role. Archives of disease in childhood 2017; **102(9):** 858-63. https://doi.org/10.1136/archdischild-2016-312001

2 Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM — Tuberous sclerosis complex: review based on new diagnostic criteria. *An Bras Dermatol* 2018; **93(3):** 323-331. doi:10.1590/abd1806-4841.20186972 (Diagnostic criteria journal)

Medical History

Native Medical Institution : The first footprint of British Medical Education in India

Rudrajit Paul[1]

28th January is celebrated as the foundation day of **Medical College, Kolkata**. This was the first medical college for the western system of medical education in Asia. It was founded in 1835. This college has been the pioneer in medical education and research in India (with a lot of firsts like the first human cadaver dissection and the first female student)for the first few decadesafter its inception, before other similar colleges came up in other parts of India. *Thus, this institution is considered a symbol of not only medical education but also, modern education as a whole in Asia*. However, Medical College Kolkata was not the first medical institution set up by the British East India government. Before this legendary college, there was another short-lived institution, the **Native Medical Institution (NMI).** This article will be a brief description of that institution primarily, with some tidbits about Medical College Calcutta towards the end.

The NMI was a short lived college, existing between 1822 and 1835 in Kolkata. During this period, the British government pursued the policy of combining eastern and western systems of medical education. So, at the NMI, the western scientific medicine was taught along with the traditional Indian systems like Ayurveda (further elaboration later). This institution received some help from the government although most of its funding came from local feudal lords (called Zamindars). *But what was the need of this new school?*

After the East India Company gained its foothold in India, they started setting up a health system (mainly for the benefit of their troops and European colonists). Before British rule, the very concept of "hospital" was almost absent from the Indian subcontinent. The only hospitals could be found in isolated European establishments like Goa. People were treated by indigenous healers, who used a mixture of herbal or metal powder based remedies along with a strong dose of religious chants and amulets. People almost entirely were born and died in their own homes. Certain diseases like leprosy or syphilis would make the people social outcasts and they would be forced to live in the forests or bushes and die a slow painful death. After the East India Company established its rule, they felt that modern scientific treatment centers were urgently needed both for themselves and also the natives. But one major problem was the dearth of physicians trained in the scientific medical system. At first, British doctors were brought to this colony;but that started to prove too cumbersome and costly. Thus, soon the British colonists realized the need to train local students in medicine. Even if these students would not be allowed to directly treat the Europeans, at least they could act as assistants/dressers to the European doctors. On 9th May, 1822, at the official meeting of the Bengal Presidency, a plan to train local students to create doctors and fill up the vacancies of the government hospital posts was discussed. The secretary of the Calcutta Medical Board proposed setting up an institution urgently.

On June 21, 1822, the NMI was established in Calcutta with 20 students vide Governor General's order no. 41. A European doctor (civil assistant surgeon) was placed in charge with two native assistants. The first students were taught treatises on Anatomy, Medicine and Surgery, which had been translated into local language from European texts directly. Teaching was done in local languages. Before arrival of the British rulers, Persian was the official language in India (since the Mughals had come from the Middle East). *Thus, Persian and Urdu were included as teaching media*. (Bengali was probably not included as a teaching medium because in those days, before Iswarchandra Vidyasagar, Bengali was probably not developed enough to be considered an academic language) Local Sanskrit scholars were paid handsomely to translate English texts. After establishment of this medical institution, the Sanskrit college was established in 1824. From 1826 onwards, classes on Unani and Ayurveda were added. These classes were held at the Calcutta Madrasa and Sanskrit College respectively and were taught by teachers associated with those colleges. At Sanskrit college, the Charaka and

[1]MD, DNB, MRCP (UK), Consultant Physician, Kolkata

sushrutaSanhitas were taught while the Madrassa discussed Arabic medical texts of Avicenna. Dr John Tytler was the most famous superintendent of NMI (1830) (although not the first) and was a passionate teacher. He was a surgeon in Indian Medical Service and a passionate orientalist. He was one of the proposers of the NMI and it would have been natural for him to become its first superintendent. But he decided not to contest for the post as he was posted in Munger at that time and only at the end of 1830, when Peter Breton died, he was given the post at NMI.

This institution was not associated with any hospital. The main reason being that hospitals were very scarce in India at that time, let alone a hospital for teaching purposes. Thus, the students were required to visit other hospitals and dispensaries to gain clinical experience. However, there were no hands-on classes in anatomy. *The NMI days saw the first introduction of European instruments like Stethoscope and Thermometer to Indian students*. Also, another important feature of the NMI education was the maintaining of case records of patients. Before this British system of education, the traditional Indian medical system did not have any system of scientific recording of patients' signs and symptoms. At the NMI, the first doctors were taught how to keep history of patients and later, deduce the diagnosis by analyzing the history.

Two British doctors struggled hard to establish the NMI. They were Peter Breton and John Tytler. Peter prepared a vocabulary of medical terms in local languages. He also prepared short notes on diseases like Cholera, vegetable poison and Rheumatism for native students. John Tytler tried to bring a structure to the curriculum. He stressed on chemistry lessons for a good grasp over medicines. He himself gave lectures on chemistry. The main texts used to teach students included Hooper's books and Fyfes' Manual of Chemistry. During the three year course, he taught the students "names, doses and properties of medicine they employed……the habits of attention and observation". One memorable work of Tytler was the series of lectures on the human skeleton. This led to immense popularity among the students. He also reprinted anatomical drawings from British medical texts and reproduced them in Bengali for the students (Fig 1).

The training period was three years. The first year was Physiology, Pharmacy, materiamedica and anatomy. The next two years were medicine and surgery. Students visited the Native Hospital, General Hospital, Company's Dispensary and department of

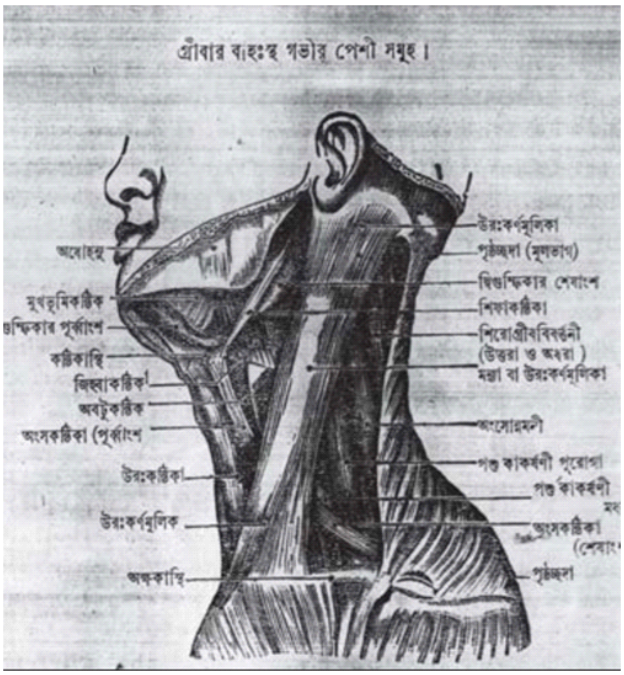


Fig 1 — An illustrated anatomical drawing in Bengali. Images like these were used at the NMI [taken from an article byJayanta Bhattacharya in the Indian journal of history of Science, 2015]

the Superintendent of Vaccination. They dissected animals like Sheep or Dog. Also they observed post mortem examination at the General Hospital (being conducted by European doctors). Later, in 1831, a small hospital was opened with 30 beds for the students. The concept of a period of apprenticeship at the end of academic classes was also introduced. So, in all, the NMI acted as the "gestation period" for the future Western Medical education. But soon, the decision to form a new Western Medical college was taken and the government did not patronize this hospital further.

According to historical records, a total of 136 doctors passed out of the NMI before it was closed. Many of the students were family members of Indian members of the British troops. They were sometimes called "black doctors" in the army. Breton, the superintendent of NMI from 1825 to 1830, noted that the Indian students accepted the teaching of anatomy with surprising enthusiasm.

Following the NMI, another similar institution called the **Indian Medical School**, was started in Bombay in 1826. But it lasted only 6 years and did not leave much impact.

However, this institution (NMI) did not last long. In 1833, the then governor of Bengal, Lord William Bentinck set up a committee consisting of Dr John Grant as President and J C C Sutherland, C E

Trevelyan, Thomas Spens, Ram Comul Sen and M J Bramley as members. [Just a word about Ram Comulsen : He was the Grandfather of Keshab Ch. Sen. He was one of the ardent opponents of Raja Rammohan Roy regarding abolition of the infamous Sati.]This committee was entrusted with the task to appraise the current status of medical education in Bengal and make its recommendations. At that time, within the British administration, a tussle had started between two groups of thinkers: *Anglicists and Orientalists*. The former group wanted to change the medieval education system of India fully and rebuild the system after European model. The latter group wanted a synthesis of western and Eastern education systems. But the Anglicists prevailed. Thus, the committee recommended abolishing the NMI and setting up a new college to teach western scientific medicine to the natives. The main medium of education would be English and all Indian indigenous medical texts would be banned. The reason for stressing on English as a medium of learning was explained thus:

"A knowledge of language we regarded as a 'sin qua non'…We wish them to be able to drink out of thefountain head instead of depending to allaytheir mental thirst with driblets oftranslation"

No traditional medical practitioners would be allowed entry into this new institution. The whole system of education would be fully European. Macaulay, an influential thinker of that era, wrote a verbose minute supporting this point of view and this finally influenced Lord Bentinck to take the final decision. On 2nd February, 1835, Mr T.B. Macaulay wrote a lengthy document fully laying out his plan for the future of the education of India under British rule. In it, he says,

"What we spend on the Arabic and Sanscrit Colleges is not merely a dead loss to the cause of truth. It is bounty-money paid to raise up champions of error. It goes to form a nest not merely of helpless placehunters but of bigots prompted alike by passion and by interest to raise a cry against every useful scheme of education."

Also, he writes:

"The languages of western Europe civilised Russia. I cannot doubt that they will do for the Hindoo what they have done for the Tartar."

Thus, a clear argument was made in favour of introducing the western system of education in all spheres, including medicine. But probably this intention of introducing Western Medicine in India was present all along. Even before Macaulay's minute, in 1834, Dr Tytler said that the British just wanted to buy time to prepare the natives for European medicine (Fig 2). *The*

European science like the Christian religion has by far the best chance of succeeding among the nations of Hindoostan by our avoiding even the appearance of coercion and allowing and even encouraging them to study their own system and ours together and quietly make the comparison themselves. We thus prove that we have no jealousy of their knowledge, we incline all their national feeling in our favour and give their understanding full room to act. . . .

Fig 2 — Comment by Dr Tyler in 1834 (taken from the book "Colonizing the body" by David Arnold)

British administrators felt that by teaching Western and Indian medical systems side by side, the people of India would automatically realize the superiority of the former and accept it willingly.

Thus, the NMI was the harbinger of the Calcutta medical college. This institution gave Indians their first taste of Western Medicine and Medical education system. But it must be remembered that although the new medical college was set up, the government did not abolish the old medical education systems. The Sanskrit college continued to receive government patronage and continued to teach Ayurvedic medicine. It was just that this indigenous system was separated from the new western medical education.

The end and a new beginning:

On 28th January, 1835, NMI was abolished by government order (No. 28, signed by Lord Bentinck) and a new college was proposed. However, the first students would be admitted later and the first buildings would come up after a few months. But since the resolution was passed on this date, the day is celebrated as the "birthday" of this Calcutta medical college. On 20th February, 1835 student admission started. The first batch had about 49 students, all aged less than 20. It was decided that the students who passed would be allowed to enter public service in the Bengal presidency. The first classes were held in an old house behind Hindu College. In May, 1835, the institution shifted to the present premises. The land was donated by a prosperous feudal lord of Bengal, Motilal Seal. The setting up of this institution signified a paradigm shift in the history of India. Before 1835, people had a tolerant attitude towards indigenous medical systems and there was academic support behind them. But after 1835, the Western system was focused as the sole valid medical system and all others were relegated to an inferior status.

Madhusudan Gupta was an Ayurvedic teacher at Sanskrit College from 1830 to 1835, who taught students of the NMI who went to Sanskrit college for some lecture classes. There, he became close to both

Tytler and Grant. When the medical college was set up, he became a teacher there. He was involved in the first ever entrance examination for the college. *Also, in 1836, he was the first Indian to dissect a human body at the Medical College*. David Hare greatly influenced him to perform this act. Prince Dwarakanath Tagore was also quite enthusiastic about anatomy dissection and helped the students a lot, including procuring nameless corpses from the streets.

The first fully constructed buildings were opened in 1836. On March 17, 1836, Dr Bramley, the first Principal, said,

"You may rely upon it, that, with whatever other faults our tenure of this country may be chargeable, that posterity will gratefully acknowledge the noblest of all our acts: The enfranchisement of native intellect from the darkness of ignorance, and the yoke of superstition which is ever its concomitant."

The *Bengal Harkara* was also quite enthusiastic about this new college. It wrote:

The opening of the new native Medical College, which took place yesterday, was very fully attended. Among the distinguished visitors were the Governor-general, the Commander-in-chief, the Members of Council, the Law Commissioners, the heads of several of the departments and several natives of rank…

The iconic MCH building (Medical College Hospital Building) was started in 1848 by Lord Dalhousie. The foundation stone was laid with great fanfare. The illustrated London News reported the ceremony and even printed an illustration of the event (Fig 3).

So, it must be remembered that the Native Medical Institution was set up even before Sanskrit College and other such institutions of India. But sadly, this institution is totally forgotten in the later Indian history texts. Historians of independent India, while extolling the virtues of Sanskrit College and Hindu College, often chose to delete the name of NMI from standard texts.

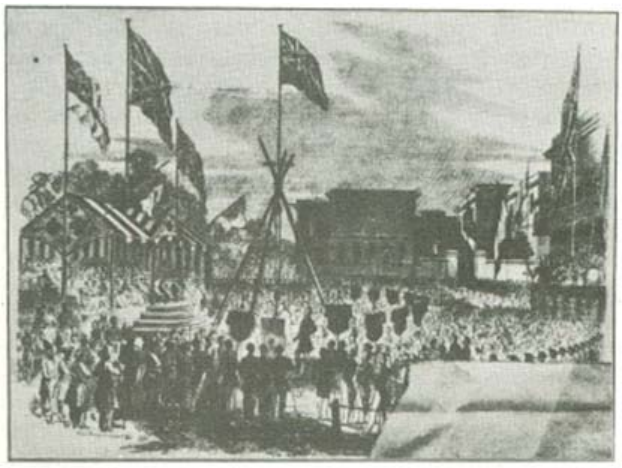


Fig 3 — Foundation stone laying of MCH building: Artists' impression, 1849, London

The author of this article (Rudrajit Paul) had to get the data for this article mostly from foreign texts as Indian authors have a culture of silence about this pioneering institution.

Further reading :

1 Khaleeli Z. Harmony or hegemony? The rise and fall of the native medical institution, Calcutta, 1822-35. South Asia Res. 2001;21(1):77-104
2 Bandyopadhyay K. Looking back at the oldest surviving block in Asia's medical history. The Times of India. [Published 2018 Oct 4; Cited 2021 Jan 03]. Available online from https://timesofindia.indiatimes.com/city/kolkata/looking-back-at-the-oldest-surviving-block-in-asias-medical-history/articleshow/66062483.cms
3 Kumbhar K. How the Calcutta Medical College Led to the Rise of Biomedicine in India. The Wire [Internet]. [Published 2019 Mar 28; cited 2021 Jan 8]. Available online from https://thewire.in/health/east-india-companys-need-for-military-doctors-brought-modern-medicine-to-india
4 Hochmuth C. Patterns of Medical Culture in Colonial Bengal, 1835-1880. Bulletin of the History of Medicine 2006; 80: 39-72
5 Kumar D. Medical Encounters in British India, 1820-1920. Economic and Political Weekly 1997; 32: 166-70

Perspective

How to Conduct Clinical Trial during an Epidemic : Lessons from the WHO Solidarity Trial

Rudrajit Paul[1], Jyotirmoy Pal[2]

The Covid-19 pandemic has been the greatest challenge facing doctors and scientists over the last one year. This new virus with no known therapy or vaccine wreaked havoc all over the world with high mortality among the elderly and those with certain chronic conditions. In March 2020, the World Health Organization (WHO) started an international trial on treatment options for Covid-19: **Solidarity.** An interim result was published in the NEJM on December 2, 2020. The process of conducting this trial during on emerging pandemic is a good case study for future medical researchers. Here, certain salient points of this trial will be highlighted.

The trial was essentially started with four drugs: Remdesivir, Hydroxychloroquine, Lopinavir and Interferon beta-1a. These are drugs, already in use for other indications, which had been repurposed for Covid-19 based on expert opinion. But design of the trial was adaptive. This means that during the trial, any drug found useless could be dropped and any other molecule found or thought useful could be added. Thus, the end point of the trial was not defined by the clinical efficacy of one particular drug but rather, clinical improvement of the patient (by whatever means) was the sole purpose. This is in sharp contrast to usual clinical trials where the effects of one particular drug is analysed for a long time.

Technology came in handy during recruitment for this trial. A cloud based data management system was used which also factored in local availability of the trial drug(s) before assigning a study subject to a particular arm of therapy. Thus, the need to spend time on procuring a particular drug for the trial was avoided.

Very quickly, it became clear that some of the drugs were useless. Thus, HCQS, Lopinavir and Interferon arms were discontinued on June 19, July 4 and October 16 respectively. So, wastage of valuable time in experimenting with futile therapies could be avoided. During an epidemic, there is no time to do finer sub-group analysis. If anything is not showing significant clinical result within a short time, it must be abandoned and other options looked for.

This trial had no placebos. Participants either received one of the four drugs or they just received standard supportive therapy without any trial medicine. Thus, during a medical emergency, the standard protocol of blinding or using placebo as control was skipped to save time. Since the drugs had different formulations (oral or iv) both the doctor and the patient knew which therapy was being tried. The main aim was to see whether lives are saved, not to eliminate observers' bias.

For any clinical trial, sample size is very important to give the study adequate power. But during an emerging epidemic, when the probable number of persons infected is essentially unknown, this method of calculating sample size is not useful. Thus, in this trial, the WHO steering committee said,

"The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops. …"

Finally, during an epidemic or pandemic, different trials are simultaneously conducted at multiple centres. So, another crucial question arises.How to synthesize these data together? Since all the studies are started on an emergency basis, it is likely that there will be very little homogeneity among the study methodology in different countries. In the Solidarity trial, they used inverse-variance–weighted average of $b=\log_e$ rate ratio from each stratum of each trial.

One major impact of this Trial result publication was stopping similar trials elsewhere. Thus, wastage of time and money on futile therapies could be stopped. During an epidemic, when the allocation of funds is of prime importance, the results of such trials are important in choosing the future direction.

References

1 WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. NEJM 2020; [Online First December 2, 2020]. DOI: 10.1056/NEJMoa2023184

[1]MD, DNB, MRCP (UK), Consultant Physician, Kolkata
[2]MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Professor of Medicine, RG Kar Medical College & Hospital, Kolkata 700004

History : Remembering the Stalwarts

Rudrajit Paul[1], Jyotirmoy Pal[2]

Waldemar Haffkine was not a medical doctor. But we should remember him because he did pioneering work in vaccine research during the epidemics of India at the turn of the nineteenth century. The two major epidemics ravaging India at that time were Cholera and Bubonic Plague. Cholera was already an established menace for India with cases throughout the year and occasional explosive outbreaks during large public events like the Kumbha Mela. Plague epidemic came to India in 1896 from Hong Kong and marched through large parts of the country. In an era when public health was still in infancy and antibiotics were still unheard of, the only ray of hope was the vaccine.

Haffkine, an immigrant from Ukraine, had worked in the famous Pasteur Institute of Paris and developed a Cholera Vaccine. He had injected himself with the first doses to be sure of its safety. Then, Lord Dufferin, the British ambassador to France and a former viceroy to India advised him to go to Bengal, the then hotbed of Cholera epidemics. Haffkine came to the then British capital of Calcutta in 1894 and started is inoculation program. After initial resistance, the common people were highly receptive of this new technology. He then also inoculated the slaves in tea plantations of Assam.

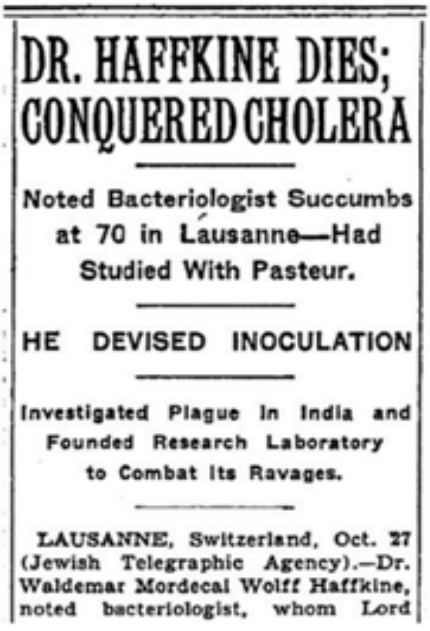
In 1896, Haffkine started work on a new vaccine for Plague. By 1897, his vaccine was ready. Again, he injected himself first to be sure of its safety. When a plague outbreak occurred in the Byculla prison of Bombay, he performed mass vaccinations there. Initial results were encouraging and the government allowed him to inoculate thousands of people all over the country. He was made the director of a new plague research laboratory in Bombay and the British government provided him with a lot of funding.

But one mishap happened in 1902 which tarnished his efforts. A small outbreak of tetanus occurred among the recipients of the vaccine in just one village of Punjab. But this incident caused immense public outcry and the government took the drastic step of suspending Haffkine. Later investigation revealed that the tetanus outbreak was not his fault but it happened due to carelessness of one health worker.

Later, Haffkine returned to Calcutta again to work as a scientist. But he could never overcome the stigma of the mishap. He died in Switzerland (Fig 1).

Waldemar Mordechai Wolff Haffkine

This image is available via National Data Sharing and Accessibility Policy (NDSAP) of Government of India



DR. HAFFKINE DIES; CONQUERED CHOLERA

Noted Bacteriologist Succumbs at 70 in Lausanne—Had Studied With Pasteur.

HE DEVISED INOCULATION

Investigated Plague in India and Founded Research Laboratory to Combat Its Ravages.

LAUSANNE, Switzerland, Oct. 27 (Jewish Telegraphic Agency).—Dr. Waldemar Mordecai Wolff Haffkine, noted bacteriologist, whom Lord

Fig 1 — This picture taken from BBC website

[1]MD, DNB, MRCP (UK), Consultant Physician, Kolkata
[2]MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Professor of Medicine, RG Kar Medical College & Hospital, Kolkata 700004

Mediquiz - 01 / 2021

Editor introduced a regular Quiz Section for brainstorming of the readers. We shall highly appreciate your participation. Your aptitude and knowledge will be acknowledged with prizes for the correct entries. Please send us your response by the deadline. In case of tie, there will be a draw of luck to decide the winners as the number of prizes are limited. We shall also appreciate your feedback on this section. Good luck!

Kausik Ray, Sandip Kr Halder
Consultant Surgeon, Dr Gray's Hospital, Elgin, UK

Gastrointestinalsymptoms are the commonest presentations of our patients. Patients present to doctors with gastrointestinalsymptoms to the doctors across the medical andsurgical specialties. Awareness of gastrointestinal diseases is quite useful for all the doctors to investigate and treat the patients and also to refer them to the appropriate specialists.

The theme of the quiz of this issue is Gastrointestinal System

(1) Which of the following statements is incorrect? —

a. Retrosternal goitre can cause dysphagia by extraluminal pressure on the oesophagus

b. Achalasia cardia causes dysphagia to liquids

c. Anti-reflux surgery helps in symptoms of dysphagia

d. GISTs often present with dysphagia possibly originates from the 'pacemaker cells of Cajal'

(2) **Following statements are true regarding 'Gastro-Oesophageal Reflux Disease' (GORD) except: —**

a. Unabated GORD may lead to the development of Barrett's oesophagus and rarely to adenocarcinoma

b. GORD is commonly associated with paraoesophageal Hiatus Hernia

c. Anti-reflux surgery restores the natural valvular mechanism against refluxto oeaophagus

d. Monitoring 24 hours pH and Lower EsophagealSphincteric pressure are imperative before anti-reflux surgery

(3) Which of the following statements about upper gastrointestinal bleeding is not correct? —

a. Variceal bleeding is associated with uncontrolled Portal Hypertension

b.Rockall scoring states that the score less than 3 has less chance of rebleeding for 'Non-variceal' bleeding

c.Sengstaken-Blakemore tube can be used to control both oesophageal varices and duodenal ulcer bleeding as it has two separate balloon system

d. Interventional Radiologist targets Gastro-duodenal artery for embolization in uncontrolled duodenal ulcer bleeding

(4) Which statement regarding oesophageal canceris not correct? —

a. Smoking, alcohol consumption, corrosive ingestion, overweight and Barrett's oesophagus are all known risk factors

b. Adenocarcinoma is more common variant in the western world and usually affects the middle third of the oesophagus

c. Endoluminal Ultrasound and CT scan of thorax and abdomen are essential adjuncts of management

d. 'Ivor-Lewis' Oesophagectomy is approached from both abdominal and thoracic route

(5) Following are the 'Red-flag Signs' for 'two-week referral' to Endoscopy unit for excluding gastric cancer, except –

a.Progressive unintentional weight loss

b.Increased apatite and acid reflux

c.Iron deficiency anaemia

d.Epigastricmass

(6) Following statements are correct regarding gallbladder and related problems, except—

a. Cholesterol stones are formed due to over-secretion of cholesterol in bile, decreased bile acid concentration, andhypomotility of gallbladder

b. A passing stone through Ampulla of Vater can produce cholangitis, pancreatitis and obstructive jaundice

c. Ultrasonography is the gold-standard primary radiological investigation for the gallstone related conditions

d. Calot's triangle is formed by Inferior border of the liver, Cystic duct and Common Bile Duct and contains cystic artery and cystic lymph node of Lund

(7) Disorders that increase risk for chronic pancreatitis include all of the following except:

a. Cystic fibrosis

b. Hypercalcemia

c. Excessive alcohol consumption

d. Hyperthyroidism

(8) Which statement is incorrect regarding lower GI bleeding? —

a. In elderly patients, diverticular bleeding is common and stops spontaneously most of the time

b. Grade III and Grade IV haemorrhoids with bleeding need operative intervention

c. 'Pseudopolyps' are seen in Ulcerative colitis and 'Cobble-stone appearance' is the characteristic of Crohn's disease

d. Ulcerative colitis affects caecum and ileo-caecal junction commonly

e. Watershed line of blood-supply is the reason of Ischemic colitis at the splenic flexure

(9) Regarding colonic diseases the following are true, except —

a. Familial Adenomatus Polyposis (FAP) and Lynch Syndrome are genetically transmitted conditions related to Colo-Rectal Cancer

b. Usually theright sided colonic cancers present with anaemia and left sided ones present with obstruction usually

c. In Ulcerative colitis, the risk of colonic cancer after 10 years increases with 2%/year and reaches about 25% after 20 years

d. MRI pelvis is an optional investigation for rectal cancer staging as it does not significantly affect the course of management of the disease

(10) Regarding ano-rectal diseases,which of the following statements is false? —

a.Grade IV piles may mimic rectal prolapse

b. Full thickness rectal prolapse entails pelvic floor weakness and external sphincteric defect

c. 'Goodsall's rule' is applied for Haemorrhoidal classification

d. Lifestyle modificationand GTN cream use help fissure

Answer : Number 7 d

Answers for the rest as above to be sent to the Editor before at midnight 05-02-2021 e-mail : jimaeditorial@gmail.com

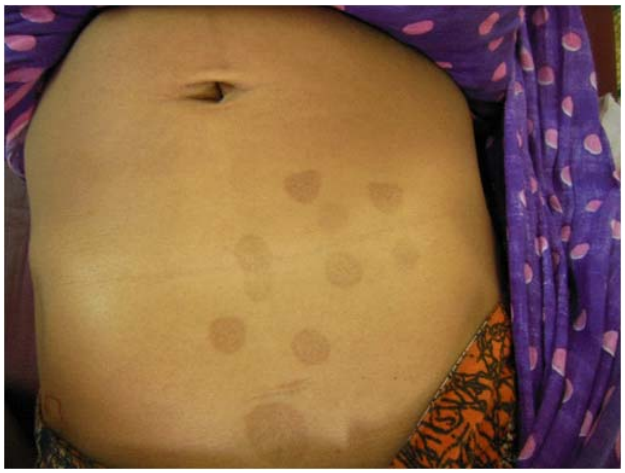
Please mention : Your Name, e-mail id, Mobile No & IMA Membership No.

A 48 year old lady presented with non specifica abdominal pain and had multiple consultations over last 10 years from various alterntative medicine practioner.On examination of abdomen what is this peculiar skin marking attributed to alternative medicine treatment called as ?

Ans : CUPPING

Also called Hijama therapy/cupping/chapan therapyor Horn treatment is a popular alternative medicine procedure used to alleviative multiple symptoms(mostly not attributed to a specific diagnosis).The widespread use across the world suggests the popularity.In this technique a Vacuum cup is placed across the surface/May be replaced by a Hot coin placement to produce a patterned abrasion.A "wet" variant use Dermabrasion with collection of Blood in the "cup" to remove "toxins".Disease transmission such a Hepatitis etc make it an dangerous procedure if bloodletting is combined with cupping.Superficial bruise in patients with Oral anticoagulants and skin infections are common side effects.

Knowledge of these findings for practioners in developing countries where the history of seeking alternative



medicine is ususlly masked should be encouraged to avoid clinical dilemma.

Professor S Das,
Professor, Department of Surgery,
RG Kar Medical College, Kolkata 700004

Special Article

Understanding whole grain awareness and consumption in select Indian cohorts

Jagmeet Madan[1], Naaznin Hussain[2], Shilpa Joshi[3], Joshya Mehra[4], Ankita Marwaha[5], Richa Bharti[6], Joel Thomas[7]

Background and Introduction:Grains are an integral part of Indian diet. Carbohydrates constitute to 60-70% of total daily calorie intake and grains are the key carbohydrate source. Including whole grains(WG) in the diet for its health benefits is recommended in dietary guidance around the world. There is consistent evidence to support existence of barriers to WG consumption in Indian population but limited evidence assessing their level of awareness and knowledge on WG.Thus, an independent survey was designed for assessing the level of awareness and consumption of WG amongst millennials and nutritionist and dieticians.

Data collection and analysis:Tool employed was self-developed questionnaire. SPSS software and MS Excel were used for analysing data.

Results:Only 2% of the surveyed millennials were aware of all aspects of WG.Nutritionists and dieticians showed better responses than millennials. Daily WG consumption in millennials was less than 10% (42 g/day) compared to total grain consumption (432g/day) across food categories. 50% nutritionists and dieticians consume oats for breakfast.

Conclusion:

Results highlight the importance of raising awareness on the knowledge and consumption of WG amongst urban Indian millennials. It also emphasises the need of national recommendations, encouraging consumers to make half of their total grain consumption as WG. A WG stamp from FSSAI for identification of products with considerable amount of WG and campaigns with public-private partnership supported by nutritionist, dietitians, culinary experts can further help in attaining the goal of a WG rich “Sustainable Healthy Diet” for a healthy living.

[*J Indian Med Assoc* 2021; **119(1):** 88-94]

Key words **: Dieticians, Nutritionists, Urban millennials, Whole grains.**

Whole grains became a part of the human diet about 10,000 years ago. Grains are an integral part of Indian diet. Carbohydrates constitute to 60-70% of total daily calorie intake and grains are the key carbohydrate source[1]. Including whole grains (WG) in the diet is recommended in various international dietary guidance due to its association with increased health benefits and reduced risk of chronic disease. Whole grains consist of the intact, ground, cracked or ûaked fruit of the grains where the primary components (bran, germ, endosperm) are retained within their natural ratio [(2)] whereas refined grains contain only the endosperm. Whole grains are known for their high fibre, nutrients and bioactive compounds like high concentrations of vitamins; basic amino acids and numerous phytochemicals (antioxidants) which are mainly found in the bran and germ[3]. Micronutrients and phytonutrients that are present in whole grains play a crucial role in several metabolic pathways that aid in optimal immune function[4]. Oats and barley exhibit higher beneficial effect in reducing total and LDL cholesterol (3-8% reduction) in people with elevated lipid levels due to their soluble fibre content[5].

Processing especially refining and polishing of the grains reduces their nutritive value and the healthfulness[6-8]. Hence, it is recommended to consume intact whole grains as a part of one’s daily diet.

Eating a variety and replacing half of the grains consumed daily with whole grains has therefore been recommended by various international guidelines like Whole grain council, 2015-2020 Dietary Guidelines for

[1]PhD foods and Nutrtion,Professor and Principal, Sir VithaldasThackersey College of Home Science (Autonomous) SNDT Women’s University, Mumbai

[2]PG Dietetics, Founder - Freedom Wellness Management

[3]MSc, RD, Independent Practicing Dietitian, Private Dieticianconsultant Dietetian and Diabetes Educator

[4]B Tech, Assistant Manager, Pepsi Co India Holdings Private Limited, Haryana

[5]PG Diploma in Clinical Research, Associate Director- Health & Nutrition Science, PepsiCo India Holdings Private Limited, Haryana

[6]MSc Food Science and Technology, Manager- R&D Health & Nutrition Science, PepsiCo India Holdings Private Limited, Haryana and Corresponding Author

[7]MBA, Manager, Euromonitor International Consulting

Americans (DGA), and summary report of the EAT-Lancet Commission[9-11].To achieve planetary healthy diets by 2050, Eat-Lancet recommends[12], increased consumption of plant-based foods-including whole grains ie, 232 g of whole grains intake per day in a 2500kcal diet.

In a study by V. Mohan et.al conducted in urban population of Chennai, India [13] it was found that refined cereals contributed to the bulk of the energy (45.8%), followed by visible fats and oils (12.4%) and pulses and legumes (7.8%). This evidently highlights that majority of energy requirement of Indian population is derived through refined cereals.

There is also consistent evidence to support existence of barriers[14,15] to whole grain consumption. In a study by Vasudevan Sudha, author concluded that cooking quality and appearance of the grains were perceived as the most important factors to consider when purchasing rice among Chennai urban adults[14]. Other probable reasons contributing to low consumption of whole grains could be difficulty in identifying foods that contain whole grains, availability, palatability, high price, long cooking time or lack of strong and consistent messages that clearly communicate to the public the health benefits of eating more whole grains[16]. We also see, limited evidence of studies conducted to assess the level of awareness and knowledge on wholegrains amongst Indian population.

Thus, we decided to conduct 2 independent surveys amongst urban Indian population namely, millennials (consumers) and nutritionists and dieticians to assess the level of awareness of whole grains & estimated consumption of whole grains. The millennial population was targeted as they are more likely to drive consumption[17] and can influence their peers as well as the upcoming generation. The urban millennial group in India constitutes 33% (at 450 million) of the country's total millennial population[18].

We decided to include nutritionists and dieticians as one separate cohort considering their expertise in the field of nutrition. This was deemed to be necessary as the incidences of life style disorders are on the rise and hence people prefer professional assistance for diet recommendations.

Materials and Methods

Sample Selection :

This cross-sectional study was focused on understanding the awareness and consumption of whole grains in 2 cohorts, namely urban millennials (consumers) and nutritionists and dieticians.

Study Methodology :

For millennials this survey was conducted in 4 metro cities namely Delhi, Mumbai, Kolkata and Chennai from March 2018 to April 2018. For sample size selection, factors considered were a confidence level of 95%, confidence interval of 3, income status primarily focusing on middle income group. The estimated sample size was calculated based on the total population of millennials, aged 18 to 40 years in India (n = 463,920,049), derived from the Population Enumeration Data 2011, published by the Government of India [19]. A total of 1,000 millennials were selected as the final sample size in equal proportion across each of the four metropolitan regions (n =250 each). A standardized ratio of 1:1 for gender was used to determine the number of males and females in the selected sample. Data collection tool employed in this survey was a self-developed questionnaire administered online. Questionnaire was developed to understand awareness & consumption of participants along with basic information on demographic parameters like age and gender. The awareness questions captured data across 4 key elements; understanding of whole grain concept, benefits of consuming whole grain, recommended whole grain intake and awareness regarding food items containing whole grain. Questions on consumption included amount and frequency of whole grains consumed. The questionnaire used to gather inputs from the millennials was validated prior to survey by Euromonitor (leading global provider of market research), in-house survey experts, and with top independent nutritionists and dieticians from the country (eg, National Institute of Nutrition (NIN), Indian Dietetic Association (IDA), etc.) for the relevance and accuracy of questions concerning awareness and consumption of wholegrains in India. The survey was initially piloted among a sample of 100 millennials across the four cities, to test responses and check for any issues with the survey being run online, before carrying it out with the complete sample. Questionnaire was a blend of open and close ended questions.

Online surveys were distributed to consumers through leading panel providers who abide by the ICC / ESOMAR[20] code for ethical market research.

Respondents were screened to ensure pre-defined, nested quotas are met. These quotas were typically set to match the broader population of the country in terms of age and gender and consent from consumers / their agreement to specific terms and conditions while signing was taken.

For the second cohort of nutritionists and dieticians, structured pre validated questionnaire was used. Questionnaire was mainly designed to cover the aspects such as awareness on whole grains along with its benefits, recommended daily intake and consumption by the participants. Participants who voluntarily filled the forms were included in the survey. This survey conducted in December 2017 comprised of participants from various metro and non-metro cities and included practicing nutritionists and dieticians. From a total of 310 participants, 94% were females.

Statistical Analysis :

SPSS and MS Excel software were leveraged for analysing millennials data while only MS Excel was leveraged in case of nutritionists and dieticians. MS Excel was primarily used for frequency distribution analysis, while Statistical Package for Social Sciences statistical software package version 20.0 (SPSS Inc., Chicago, IL, USA) (SPSS) was used for conducting detailed analysis especially for determining the consumption of whole grains from different food types. Descriptive statistics were carried out; not inferential statistics.

Categorical data were presented as number and percentage. Continuous data were presented as mean. Univariate analyses were carried out using descriptive statistics. Since millennial survey was an online survey, there was the risk that participants could refer to published material online to answer the questions. All responses which were a direct replica of standard definition available online were thus considered to be outliers and removed from the dataset, before running the analysis.

Since not all questions in all the surveys were mandatory to answer, hence the sample numbers differ for different questions, and analysis was done based on the number of participants answering a particular question.

Results :

This survey focused on assessing awareness and consumption of whole grains in selected cohorts of the study. A sample size of 1000 millennials (250 from each of the 4 metro cities) and 310 nutritionists and dieticians (from 4 metro cities and other tier 2 cities) completed this study. The demographic data collected for two cohorts under investigation revealed that maximum (45%) millennials were in the age group 31-35 years and had reasonable purchasing power considering the income data available. For nutritionists and dieticians 48% were in the age group 20-30 years while 31% were in the age group 31-40 years.

As discussed in the methods section, the survey was conducted using separate methodologies for each of the two cohorts.

As indicated in Table 1, the extent of awareness on whole grains in millennials was studied across 4 key elements understanding of whole grain concept, benefits of consuming whole grain, recommended whole grain intake and awareness regarding food items containing whole grain.

Findings suggest a lack of consistency in response to all 4 elements. Considering this variation, we decided to analyse certain crucial questions from each of the 4 elements, in a consolidated manner. The primary outcome was that only 2% (15 out of 1000) millennials were aware regarding the concept of whole grain in all respects.

In the millennial population, 86% participants believed that they were aware of the term wholegrain but, only 5.4% correctly responded to the question related to composition of wholegrain. This clearly reflects the gap in the understanding of the concept of whole grains. Regarding the health benefits of whole grains, 71% millennials mentioned that whole grains offer superior nutritional benefits compared to refined grains. However, on an average only 47% participants could correctly identify the specific health benefits. This points towards the lack of awareness in terms of health benefits of wholegrains. Further, only 44% of millennials aptly identified 48g or 3 table spoon to be the minimum recommended quantity of whole grains to be consumed in a day.

This disparity in the responses strongly highlights the need for focused efforts in increasing awareness with respect to understanding of whole grains and recommended intake of whole grains among millennials.

When similar survey and analysis was done for the second cohort comprising of, nutritionists and

Table 1 — *Whole grain Awareness survey in millennials and nutritionists and dieticians*

Questions	Millennials	Nutritionists and dieticians
Understanding of whole grain concept		
Are you aware about the term 'whole grains'?	86% were aware	100% were aware
If you are aware about whole grains, what do you understand about whole grains?	5.4% defined correctly	40% defined correctly
Understanding regarding whole grain benefits		
Whole grains offer superior nutritional benefits compared to refined grains	71% Agreed 10% Disagreed 19% mentioned both to be similar in nutritional benefits	100% Agreed
Which among the following are the benefits of consuming whole grains?	On an average 47% answered correctly	Average 77% answered correctly
Recommended whole grain intake		
Are you aware of the minimum amount of whole grain one needs to consume in a day?/ How many grams are in one serving of whole grains?/ How many minimum servings of whole grains one needs to consume in a day?	44% said 48g or 3 tbsp 56% answered other than 48g or 3 tbsp	54% answered 32g in one serving 43% answered 3 servings
Awareness regarding food items containing whole grain		
Please select all the foods you believe contain whole grains, from the list / Which of these are made up of whole grains?	70.1% said brown rice 64.1% said Oats Rotis with multi grain ata 61.0% Brown bread 52.7% Corn flakes 41.2% White flour 37.0%	56% said Dalia
Do you believe foods that are enriched / fortified, provide the same benefits as whole grain foods?	53% said Yes	

dieticians, their responses as seen in Table 1 were found to be better than the first cohort of millennials. This describes the impact education can have on awareness. 40% nutritionist and dieticians correctly defined whole grains. Further, 54% correctly answered the questions based on number of grams present in one serving of whole grain and 56% participants were able to correctly identify the food that contained whole grains from the total list of foods made available to them. A very high percentage of participants in this cohort agreed to oats being a good source of fibre (99%) and 70% considered it to be a super grain.

The overall findings on awareness in both the cohorts reinforces the need for suitable Indian guidelines on wholegrain intake and recommendation on serve sizes, both of which could be considered as reference standard for awareness and can also drive the consumption of whole grains.

As a second objective of this survey, wholegrain consumption in both the cohorts was also studied. Tables 2 and 3 describes consumption behaviour in millennials and nutritionist and dieticians, respectively.

It was found that 64% of millennials believed that they consume adequate amounts of wholegrain. To verify the same, analysis of further questions namely means to measure the quantity of whole grains, amount of whole grain consumption from refined and/or processed foods and amount of consumption of grains in the whole form was performed. However, results based on actual calculated daily grain consumption showed that whole grain consumption per day in millennials was less than 10% (42 g/day) when compared to total grain consumption (432g/day) across food categories (Fig 1). It was also found that average whole grain consumption per day from processed foods in this cohort was merely 5.85 g/day and 36.3g/day from unprocessed food. Low average consumption of whole grains from the millennial survey emphasises

Table 2 — *Whole grain Consumption survey in millennials*

Understanding of whole grain consumption by millennials	
In your opinion, are you consuming sufficient amount of whole grain foods?	64% Yes 7% No 29% Not sure
If your answer to question 1 is Yes, how do you measure your consumption?	25% measure each intake using measuring cup/spoon
If your answer to question 1 is No, do you intend to increase your consumption of whole grain foods?	91% Yes
Amount of whole grain consumed	
Amount of whole grain consumption from refined and/or processed foods	5.85 g/day
Amount of consumption of grains in the whole form	36.3g/day, and driven mainly by consumption of red/black/brown rice (13.5g/day)
Which of the below listed cereals / grains do you consume in the whole form (at least once in more than 2 months)?	Corn (70%) and oats (64%) appear to be the top consumed grains in the whole form

that consumption pattern of urban millennials is driven by refined foods and limited awareness about whole grain nutrition could be one of the reasons for lesser consumption of whole grains.

The consumption data of nutritionists and dieticians shows that 50% consume oats in their breakfast. This clearly suggests positive impact of education and awareness about whole grains on increase in consumption when compared to millennials. The survey also showed that 52% of nutritionist and dieticians consume white rice daily. The barriers to wholegrain consumption could be consumer taste preferences, price, availability, and convenience. While encouraging whole-grains consumption, consumer education efforts need to place greater emphasis on the substitution of refined grains with wholegrains rather than simply adding more whole grains, and therefore more calories, to the diet[21].

To summarize, findings of survey suggest that millennials claim to be aware about whole grain foods, but understanding is limited. This clearly highlights the gap amongst millennials with respect to awareness of whole grains. The lack of sufficient awareness and thereby the limited ability to correctly identify whole grain products is one of the key constraints in

Table 3 — *Whole grain Consumption survey in Nutritionists and Dieticians*

Nutritionists consumption survey	
Understanding of whole grain consumption by consumer	
Which grain is the best nutritionally?	Average 46% opted for whole wheat and oats
Oats are good source of fibre	99% Agreed
Oats are good for the entire family.	85% Agreed
Oats are good for children.	82% Agreed
Oats are Super Grains	70% Agreed
Oats has better protein quality when compared with white rice and wheat	58% Agreed
Oats are only good for heart patients.	31% Agreed
How many times per week do you consume white rice?	52% said once daily

consumption of whole grains for this cohort. Awareness of nutritionist and dieticians is understandably better when compared with millennials. Additionally, there is scope even for them to further expand on their awareness and consumption.

Discussion

The present study, to our knowledge, is the first of its kind to assess the awareness and understanding on wholegrains amongst Indian urban millennials, nutritionist & dietitians. The study also assessed the consumption of wholegrains in this population.

Overall, the study indicates that only 2% (15 out of 1000) millennials were aware regarding the concept of whole grains in all respects. Although 86% participants believed that they were aware of the term wholegrain but, only 5.4% correctly responded to the question related to composition of wholegrain and a significant number (56%) were not aware of the minimum amount of wholegrain that needs to be consumed. 40 % nutritionist and dieticians correctly defined whole grains and 56% were able to correctly identify food that contained whole grains from the list of foods provided to them.

This clearly highlights the need for a national standard on what constitutes a “whole-grain food,” to help researchers, the food industry, regulatory authorities, and consumers to have a credible harmonized source of reference.

WGs are linked to reduced risk of obesity or weight gain; reduced risk of cardiovascular disease (CVD), including coronary heart disease (CHD), hypertension, and stroke; improved gut health and decreased risk of cancers of the upper gut; perhaps reduced risk of colorectal cancer; and lower mortality rate [22]. Research reports indicate presence of a unique

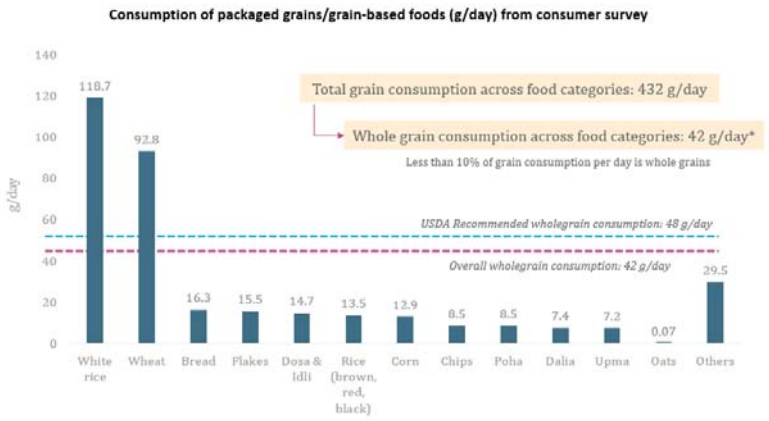


Fig 1 — Consumption by consumers in the whole form, n=1000

antioxidant, avenanthramides in whole grain oats that help protect blood vessels from the damaging effects of LDL cholesterol[23]. A deeper understanding on benefits of consuming wholegrains may help in consumer acceptance and in adoption of Eat Lancet recommended Sustainable healthy diet for a healthy living[24].

The second part of the survey was focused on assessing the consumption of wholegrains in this population. It was found that 64% of millennials stated that they consumed adequate amount of wholegrains. However, based on actual calculated daily grain consumption, out of the total grains consumed (432g/day) daily less than 10% (42 g/day) were wholegrains. The consumption data of nutritionists and dieticians show 50% consume oats in their breakfast. This clearly suggests positive impact of education and awareness about whole grains on increase in consumption when compared to millennials. 52% of nutritionist and dieticians are also seen to consume white rice daily which could be due to traditional, cultural dietary habits.

Our findings were found to be consistent with the Chennai Urban Rural Epidemiological Study (CURES)[13], 2009, Madras Diabetes Research foundation. There was high consumption of refined cereals (330.2g/day) which alone contributed 45.8% of total energy intake. Polished white rice (parboiled) was the most frequently consumed.

This further highlights the need for consumer education & probably a need for a national "Wholegrain Stamp". Global, *Whole Grains Council*[25] and a panel of scientific and culinary advisors in January 2005 created "The Whole Grain Stamp" as a visual marker to signal products that contain dietarily-significant amounts of *whole grains*. There are three different types of the Whole Grain Stamp: the 100% Stamp (*all* **its grain ingredients are** *whole* **grain**), the 50%+ Stamp (**at least half of its grain ingredients are** *whole* **grain**), and the Basic Stamp (contains at least 8g- a half serving – of whole grain but may contain more refined grain than whole). There is also minimum prerequisite of whole grain per labeled serving, for products using the 50%+ & 100% Stamp. A similar approach and stamp from Food Safety Standard authority of India for packaged foods can aid Indian consumers in making healthier grain choices.

Further in alignment to the global recommendations, National Institute of Nutrition can update the Dietary Guidelines for Indians with clear recommendations for citizens to ensure consuming half of the total grains as whole. This will translate to approximately 135-300g/day of whole grain consumption for an adult dependent on gender and activity levels. It is aligned to the recent recommendations from Eat Lancet of 232 g of whole grain intake per day in a 2500kcal diet[11,12]. Nutritionists and dieticians can assist these national bodies in carrying forward the message to consumers. Under the Eat Right India campaign, FSSAI can nudge the consumers to eat more wholegrains and amplify the message in schools, hospitals, corporates through public-private partnership.

However sensorial acceptance of any food is important for it to become a part of the daily diet. Hence, partial substitution of grains with wholegrains in any dish like combination of ragi, oats & rice to make idli, dosa, adding some additional nutrient rich wholegrains to make Indian breads (chapati, roti) could be a desirable solution to improve nutrient density and at the same time deliver to taste. Partnership with culinary institutes, chefs can further help in bringing nutritious & exciting recipes to the consumers enabling translation of theoretical knowledge to daily practice.

Conclusion :

The result of this study highlights the importance

of raising awareness on the knowledge and consumption of wholegrains amongst urban Indian millennials. It is the need of the hour to have national recommendations, encouraging consumers to ensure half of the total grains consumed are wholegrains. In addition, a whole grain stamp from Food Safety Standard Authority of India for easy identification of products with considerable amount of wholegrains and a campaign with public-private partnership supported by nutritionist, dietitians, culinary experts can further help in achieving the goal of having a whole grain rich "Sustainable Healthy Diet" for a healthy living.

Acknowledgements :

We acknowledge Saizen Global Insights & Consulting for data collection of Nutritionist and Dieticians, Jehangir Clinical Development Centre (JCDC), Pune and Dr. Arati Ranade, Medical writer, JCDC for providing technical writing service.

Conflict of Interest :

No conflicts of Interest

References

1 Misra A, Rastogi K, Joshi S. Whole Grains and Health: Perspective for Asian Indians. https://www.japi.org/february_2009/U_1.html, accessed 03/06/2020
2 Van der Kamp JW, Poutanen K, Seal CJ, Richardson, DP. The health grain deûnition of "whole grain". Food Nutr. Res. 2014; 58: doi: 10.3402/fnr. v58.22100.
3 Slavin J, Tucker M, Harriman C, Jonnalagadda SS. Whole grains: Deûnition dietary recommendations, and health benefits. Cereal Foods World. 2013; 58: 191-198. https://doi.org/10.1094/CFW-58-4-0191.
4 https://www.nin.res.in/downloads/Nutrition_Lifestyle_and_Immunity.pdf, accessed 03/06/2020.
5 Gorton Delvina, Whole Grains and the Heart: Evidence Paper 2018. The Heart Foundation, New Zealand.
6 Slavin JL, Jacobs D, Marquart L. Grain processing and nutrition. Crit Rev Food Sci Nutr. 2000; 40:309 326. doi:10.1080/10408690091189176
7 Ruxton C, Derbyshire E. The health beneûts of wholegrains and ûbre. Nutr Food Sci. 2014; 44:492-519.
8 Mohan V, Radhika G, Vijayalakshmi P and Sudha V. Can the diabetes/cardiovascular disease epidemic in India be explained, at least in part, by excess refined grain (rice) intake? Indian J. Med. Res. 2010; 131: 369-372.
9 https://wholegrainscouncil.org/whole-grains-101/whats-whole-grain-refined-grain/existing-standards-whole-grains accessed 03/06/2020
10 https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/chapter-1/a-closer-look-inside-healthy-eating-patterns/?mbid=synd_msnhealth; accessed 03/06/2020
11 https://eatforum.org/eat-lancet-commission/, accessed 03/06/2020
12 https://www.fssai.gov.in/eatlancetindia/professionals12.htmlaccessed 03/06/2020
13 Ganesan R, Sudha V, Mohan V et.al. Dietary proûle of urban adult population in South India in the context of chronic disease epidemiology (CURES – 68). Public Health Nutr. 2011; 14:591-598.
14 Vasudevan S, Donna S and Mohan V. Consumer Acceptance and Preference Study [CAPS] on Brown and Under Milled Indian Rice Varieties in Chennai, India. J Am Coll Nutr. 2013; 32: 50–57.
15 Kumar S, Mohanraj R, Sudha V, et al. Perceptions about varieties of brown rice: a qualitative study from Southern India. J Am Diet Assoc. 2011; 111:1517 1522. doi: 10.1016/j.jada.2011.07.002
16 Molika Chea, Jaime S. Foster, Jesse D. Chiero, and Amy R. Mobley. Understanding the Barriers to Whole Grain Consumption Among Low-Income Adults. The FASEB Journal. 2017; 31:956.10-956.10
17 Millennials to redefine India's consumption story: report, Updated: 20 Feb 2018, 02:48 PM IST Harveen Ahluwalia https://www.livemint.com/ dated 30/12/19.
18 https://www.kochipost.com/2019/09/17/the-invisible-rural-millennials/ accessed 27/05/2020
19 https://censusindia.gov.in/2011census/population_enumeration.html accessed 18/05/2020.
20 https://www.esomar.org/what-we-do/code-guidelines accessed 15/05/2020.
21 Nicola M. McKeown, Paul F. Jacques, et al. Whole Grains and Health: from Theory to Practice—Highlights of the Grains for Health Foundation's Whole Grains Summit 2012. The Journal of Nutrition. 2013; 143:744-758.
22 Jones M Julie, Engleson Jodi. Whole Grains: Benefits and Challenges. Advances. Annual Review of Food Science and Technology. 2010; 1: 19-40.
23 Rasane P, Jha A, Sabikhi L, Kumar A, Unnikrishnan VS. Nutritional advantages of oats and opportunities for its processing as value added foods - a review. J Food Sci Technol. 2015; 52:662 675. doi:10.1007/s13197-013-1072-1
24 EAT. EAT-Lancet Commission Report: Brief for Healthcare Professionals. 2019; https://eatforum.org/content/uploads/2019/01/EAT_brief_healthcare-professionals.pdf accessed 13/06/2020
25 https://wholegrainscouncil.org/whole-grain-stamp, *accessed 13/06/2020*

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Reorienting Medical Education in India — Absolutely Essential

Sir, — The whole objective of expansion of PG program in India should focus on achieving the final objective of MBBS seats= PG seats. We have now 80,000MBBS seats, and the available PG seats now is only 25,000. Remaining 55000 MBBS doctors can be transformed into family doctors every year starting from 2025 onwards, if we start acting now. The long-term objective must be to get 80% of all doctors working as family doctors. Increasing the number of other specialists without building a strong base for modern medicine, and without a referral system is the root cause of all unhealthy trends in India, including bridge course and the hurry to train doctors of other stream in surgery.

Background and the Issues : Heavy disease burden (due to lack of social determinants of health and wellness) and lack of good primary care in the periphery overloads the existing treatment facilities. There is no one to supervise and take charge of health and wellness scientifically and to make early diagnosis and provide decentralized disease care management. Since all patients are forced to go to tertiary care, even for their primary care, and are forced to engage multiple doctors belonging to single system specialties- without person centered care, there is a huge artificially increased need for more and more single system specialists and emergency medicine specialists. Thus, we wrongly perceive the need for more specialist doctors and more medical colleges. In reality we have enough doctors, enough MBBS seats, but we failed to produce doctors for our country, by mistake they were all being transformed only into single system specialists, ignoring all the priorities including family medicine. Specialist doctors in turn promote the centralized disease care machinery.

In the wake of Covid-19, there is a wrongly perceived need for more specialists for critical care. The suggestion of NMC to start emergency medicine, as a priority, ignoring the much needed family medicine, in each medical college has come from this wrong perception

One report of NitiAyog says India will achieve doctor population ratio of 1:1000 by 2024, but specialists shortage is huge (Dr Vinod Paul)- This statement is true only in terms of shortage of Family Medicine specialists only. As per that report India has more GPs than specialists; (Specialists: 3 lakh and Generalists 9 lakh). If we analyse the situation the 9 lakh doctors are not GPs. they are the ones who did not get a PG seat- or they are neither GPs nor Specialists- wandering desperately for a PG course. They can be labelled as NULL DOCTORS wandering and wasting time as RMOs and in PG entrance coaching centres. The Severe shortage of specialists as perceived by NitiAyog and NMC should be interpreted only as severe shortage of Family Care specialists: We produce some 50,000 'Null doctors' every year, since there are only 25000 PG seats for single system specialists every year. How can India improve with more PG seats in single system and super speciality seats without building strong base with Family doctors?

Family doctor = General Practitioner = Primary Care Specialists - all are practically the same

Who are the Family doctors? Family doctors are generalist doctors in the community setting working closer to the family providing comprehensive, continuous and whole person cantered care. A specialists in Family Medicine is someone, who had undergone proper structured training to get a degree like MD/DNB/Diploma or those MBBS doctors, who by plan wanted to practice as family doctors and had worked for three year at least, as an apprentice under good family doctors, before doing independent practice.They would make early diagnosis, because they would be aware of all the details of the individuals under their care, and this would reduce the treatment expenses phenomenally. They will also focus on health and wellness to reduce the disease burden. These generalist doctors will be accommodative and tolerant to the alternative systems and naturally avenues of cooperation would also evolve. Health and wellness to reduce morbidities will be their focus by working as friend, philosopher and guide to individuals and families. The scope for alliance with the alternative systems is possible only at the primary care level. If needed the alternative systems doctors can also be employed as primary care doctors and people should be given the choice of choosing between them. MBBS passed out doctors were all working only as GPs till 40 years ago, as they had the motivation and they developed the competence by working continuously as family doctors. Unfortunately in the present scenario they are not even primed to become GPs, they do not have the motivation and they are all primed only become specialists. The genuine need of the people for Family Medicine as a specialty, is not sensed by anyone including the MBBS students, when they are needed in large numbers. The severe shortage of specialists is true only in the context of Family Medicine specialists, the huge shortage of specialists as expressed by NitiAyog can be met only by bringing in large numbers of family doctors.

The need to Increase PG seats in India. 21 New AIIMS and 32% increase (~20,000) in 2019. Highest ever in a single year. PG(MD/MS) Seats: Record increase is commendable but they will become useful to the people only if we keep on increasing the number of family Medicine specialists. We need to declare a moratorium on increasing other PG seats till we have enough family doctors.

Our country needs large number of family doctors (a huge army of family doctors) to look after health and wellness of the people, for early diagnosis and cost effective management of diseases(including most of the emergencies) in a decentralised manner. In developed

countries up to 80% of their doctors or 80% of their health teams are working for primary care and every individual/ family has to be registered with a family doctor and the people have no right to consult specialists without referral by their family doctors. Pitiably now the affordable segment depends on tertiary care hospitals and super specialists for their primary care, that was the reason behind the artificially increased need for single system specialists. MBBS doctors waiting for PG admission are not to be counted as generalists, all our MBBS passed out doctors are aspiring to become specialists, there are very few GPs/ Family doctors now in India.

MD, FICP, FRCP **P K Sasidharan**
Former Professor & Head,
Department of Medicine, Govt. Medical College, Kozhikode

Post Stroke Epilepsy

Sir, — Post stroke epilepsy is one among the common causes of seizures in adult population. Nearly 5-20% of all individuals who have stroke will have subsequent seizures[1]. Post stroke seizures could be early or late. Early post stroke seizures occur in around 3-6% of ischemic and 10-16% of haemorrhagic stroke. Late post stroke seizures occur in around 6% of ischemic and 12% of haemorrhagic strokes over a 5-10 year follow up period[2]. There are wide variation in various studies regarding poststroke seizures due to stroke aetiology, study methodology, definitions of early and late unprovoked seizures, timing of anti-epileptic drug administration, small sample size and ambiguities in seizure identification. The risk factors for early post stroke seizures in ischemic stroke could be male population, haemorrhagic transformation, cortical location of stroke, atrial fibrillation, severestroke(NIHSS>11), partial seizures, status epilepticus and abnormal EEG[3]. The risk factors for recurrence of early seizures in haemorrhagic strokecould be cortical location, age less than 65 years, status epilepticus, hemorrhagic volume >10ml and abnormal EEG[2,3]. In the absence of RCTs a strong recommendation cannot be made on initiation of antiepileptic drugs for secondary prophylaxis of early post stroke seizures. However in practicality when antiepileptic drugs are initiated after acute symptomatic seizures, they should not be continued more than a month of therapy.

In the study by Hersdoffer et al the 10 year recurrence rate of late unprovoked seizure after one post stroke unprovoked seizure is around 70%[4]. As per the recent definition of epilepsy a single unprovoked late post stroke seizure is equivalent to post stroke epilepsy.

In this context there are certain prediction tools for assessment of seizure recurrence risks namely the CAVE score and SELECT score. In the CAVE score the following points namely cortical involvement, age <65 years, volume >10 ml and early seizures are noted and if all 4 points are present the 5 year recurrence risk of seizures in haemorrhagic stroke is around 46%[5]. Similarly in ischemic stroke the SELECT score gives a risk stratification for recurrence of unprovoked seizures following an ischemic stroke[6]. The SELECT score includes severity of stroke, large artery atherosclerosis, early seizures, cortical involvement and MCA territory involvement. The maximum score could be 9 which suggests a 5 year recurrence rate at 83%.

In the given study which is probably a descriptive study shows nearly ¾ th of patients with post stroke seizures being haemorrhagic which is slightly higher than the existing data in literature. Nearly 2/3rd of the patient developed poststroke seizures. As already pointed post stroke seizures remains the commonest cause for new onset seizures in elderly population. In the given study nearly 24 out of the 34 patients fall in the age group between 60 and 80 years of age. In the SELECT score the cortical location and MCA territory are two important variables that stratify risk. In the given study also majority of the patients with stroke had cortical involvement namely MCA territory strokes.

The above study has made certain critical cross sectional observations on the demographic/risk factors for post stroke epilepsy. However a prospective follow up study would help in elucidating more Indian data in this regard.

References

1 Silverman IE, Restrepo L, Mathews GC — Post stroke seizures. *Arch Neurol* 2002 Feb; **59(2):** 195-201.
2 Holtkamp M, Beghi E, Benninger F, Kälviäinen R, Rocamora R, Christensen H — European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. European Stroke Organisation. *Eur Stroke J* 2017 Jun; **2(2):** 103-15.
3 Mecarelli O, Pro S, Randi F, Dispenza S, Correnti A, Pulitano P, Vanacore N, *et al* — EEG patterns and epileptic seizures in acute phase stroke. *Cerebrovasc Dis* 2011; **31(2):** 191-8.
4 Hesdorffer DC, Benn EKT, Cascino GD, Hauser WA — Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* 2009 May; **50(5):** 1102-8.
5 Haapaniemi E, Strbian D, Rossi C, Putaala J, Sipi T, Mustanoja S, *et al* — The CAVE score for predicting late seizures after intracerebral hemorrhage. *Stroke* 2014 Jul; **45(7):** 1971-6.
6 Galovic M, Döhler N, Erdélyi-Canavese M, Felbecker A, Siebel P, Conrad J, *et al* — Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. Lancet Neurol. 2018 Feb;17(2):143-152

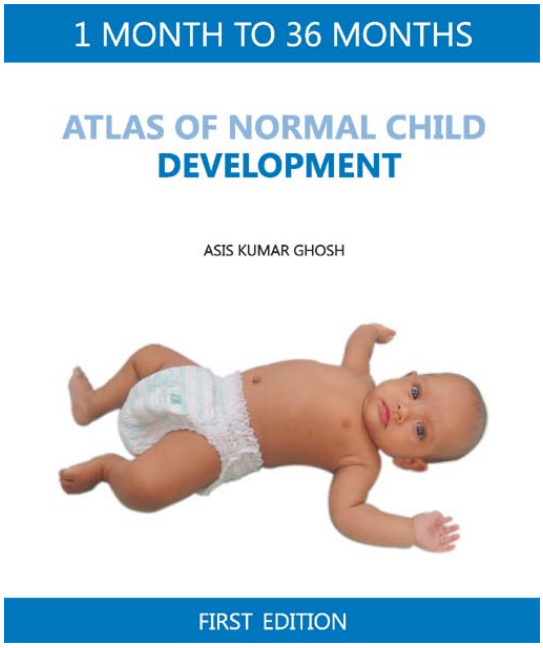
MD DM(Neuro) Fellow in Epilepsy **K Malcolm Jeyaraj**
Senior Assistant Professor
Department of Neurology
Govt. Stanley Medical College, Chennai

Sir, — **"Challenges in Medical Education in India" (JIMA, Vol 118, No 12, December, 2020)**

Very pertinent points dear Dr Vitull. Thanks to you and to JIMA for discussing this most important issue.

Prof andHead of Cardiology, **Gurpreet Singh Wander**
DAV Medical College,
Ludhiana, Punjab 141001

Book Reviews

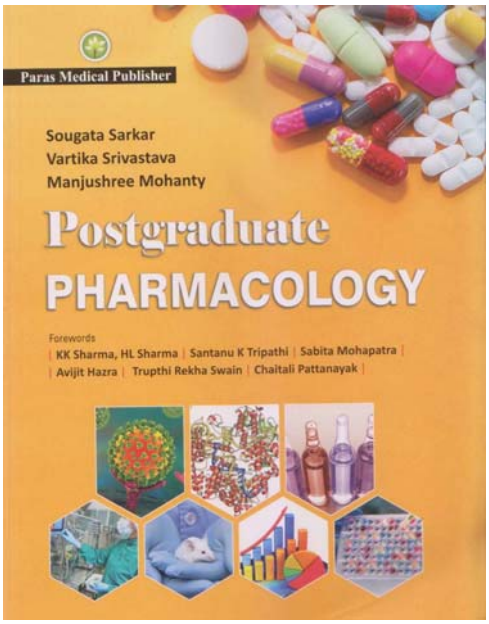


"Atlas of Normal Child Development (1 month to 36 months)" by Dr Asis Kumar Ghosh, 1st Edition, January 2016, Published by Asis Kumar Ghosh, 4E, Dr. Amal Roychowdhury Lane, Kolkata 700009, pp 1-96, Rs.500/-.

Descriptions of developmental milestones are available in any Pediatric Textbook and in most, the format is such that it promotes rote learning. What I particularly liked about the Atlas of Normal Child Development is the nuanced way the images have been captured. Readers will know exactly what to look for when they assess development in this most crucial period of 1-36 months. The picture clarity is amazing and most importantly, each developmental milestone is arranged in a holistic, sequential way and not compartmentalised. The snapshot of important milestones at the beginning of each age range will be very useful for medical students who struggle to remember all the milestones in different domains.

For novice and expert alike this book is a worthy pictorial companion to Illingworth textbook of normal development.'

Meenakshi Girish
Professor & Head
Department of Pediatrics,
All India Institute of Medical Sciences, Nagpur



"Postgraduate Pharmacology" by Sougata Sarkar, Vartika Srivastava, Manjushree Mohanty, 1st Edition, 2020, Published by Paras Medical Publisher, 5-1-475, First Floor, Putlibowli, Hyderabad 500095, Telangana, India, pp 1-634, 21.5cmx28 cm.

The goal of modern medicine is to provide palliative or permanent relief from diseases. Pharmacology plays an integral part in identification, characterization, quality control of drugs, its rational use as well as notification of adverse consequences if any. Clinical Pharmacology is indispensable in the avenues of new drug development, new treatment and its proper application in health services. Clinical Pharmacologists provide leadership in therapeutic committees and their decisions influence the prescribing governance in regional, state and national level. Keeping all these aspects in mind, the textbook, 'Postgraduate Pharmacology' authored by Sougata Sarkar, Vartika Srivastava and Manjushree Mohanty has certainly fulfilled all the criteria that a post-graduate trainee in the field of Pharmacotherapeutics should be aware of.

The chapters are well distributed, focused and informative. Various topics like drug development, clinical trials, rational drug therapy, bioinformatics, experimental pharmacology, statistics and analytical essays have been aptly discussed. Much emphasis has been given on recent advances including cancer therapy, targeted drug delivery and newly approved drugs. However, the avenues of general pharmacology like pharmacokinetics and pharmacodynamics have not been included. The pharmacotherapy of diseases as systematic pharmacology too has been partly discussed. The current drug therapy of diseases of all systems should have been highlighted to make this book foolproof for the post-graduate trainee.

Lopamudra (Dhar) Chowdhury
MBBS, DA,
MD (Pharmacology)
Professor & HOD, Dept. of Pharmacology
Murshidabad Medical College, West Bengal.
Author of
Psychiatric Drug Handbook
Pharmacology for Anesthesiologists.
It's all about lifestyle: 6 tips of lifestyle for healthy living

JIMA Guidelines for Authors

Communications intended for publication should be sent to the Editor, Journal of the Indian Medical Association (JIMA). JIMA will consider manuscripts prepared in accordance with the **Vancouver style**[1].

Articles are considered for publication on condition that these are contributed solely to JIMA, that they have not been published previously in print and are not under consideration by another publication. In the selection of papers and in regard to priority of publica-tion, the opinion of the Editor will be final. The Editor shall have the right to edit, condense, alter, rearrange or rewrite approved articles, before publication without reference to the authors concerned.

Authorship: All persons designated as authors should **qualify for authorship.** Authorship credit should be based only on **significant contributions** to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. **Conditions (a), (b) and (c) must all be met.** Authors may include explanation of each author's contribution separately.

Title page— The title page should include the title of the article which should be concise but informative, name(s) of author(s) with his/her (their) academic qualification(s) and designation(s). Declaration-regarding no conflict of interest and complete postal address including pin code of the institution(s) to which the work should be attributed. Mobile no. and email of all authors to be mentioned.

Abstract— Should carry an abstract of no more than 250 words and should contain the purposes of the study or in-vestigations, basic procedure, main findings and their implications along with **Key words and Take home message (4-5 lines).**

Text— The text of Original Articles should conform to the conventional division of Abstract, Introduction, Material and Method, Observations, Discussion, Conclusion and References. Other types of articles such as Practitioners' Series, Case Reports, Current Topics, etc., are likely to need other formats.

Statistical evaluation—Description of the statistical methods used should either be given in detail in the "Material and Method" section of the article or supportive reference may be cited.

Abbreviations— Standard abbreviations should be used and **be spelt out when first used in the text.** Abbreviations should not be used in the title or abstract.

Units of measurement— Metric units should be used in scientific contributions. If the conventional units or SI units were actually followed in measurements that should be given in parentheses.

Drugs— The **generic names of the drugs (and not proprietary names)** including dose(s), route(s) and period of administration should be mentioned.

Length of manuscripts— For Originals Articles: Maximum 2200 words, 3 figures, and/or 4 tables, for Case Reports: Maximum 800 words, 2 figures, 1 table, for Letter to the Editor: upto 500 words.

Tables— Tables should be simple, self-explanatory and should supplement and not duplicate the information given in the text.

Illustrations— Graphs, charts, diagrams or pen drawings must be drawn by professional hands. Photographs should be supplied in resolution minimum 350 dpi and 5 inch wide. In case of microphotograph, stains used and magnification should be **mentioned.** Each illustration should have a minimum resolution of 350 dpi with proper labelling. All illustrations should be with suitable legends.

References— References should be **numbered in the order in which they are first mentioned in the text.** The full list of references at the end of the communication should be arranged in the order mentioned below (names and initials of all authors and/or editors up to 6; if more than 6, list the first 6 followed by et al):

Reference from journal:

[1]Cogo A, Lensing AWA, Koopman MMW, Piovella F, Sivagusa S, Wells PS, *et al* —Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein throm-bosis: prospective cohort study. *BMJ* 1998; **316:** 17-20.

Reference from book:

[2]Handin RI— Bleeding and thrombosis. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, et al editors—Harrison's Principles of Internal Medicine. Vol 1. 12th ed. New York: Mc Graw Hill Inc, 1991: 348-53.

Reference from electronic media:

[3]National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18.

Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. **The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.**

Dual publication: If material in a submitted article has been published previously or is to appear in part or whole in another publication, the Editor must be informed.

Forwarding letter: The covering letter accompanying the article should contain the name, complete postal address along with Mobile number & E-mail identity of one author as correspondent and must be digitally signed by all authors. The correspondent author should notify change of address, if any, in time.

Declaration: A declaration should be submitted stating that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under the present authorship has been published or is being considered for publication elsewhere and the authorship of this article will not be contested by any one whose name (s) is/are not listed here, and that **the order of authorship as placed in the manuscript is final and accepted by the co-authors.** Declarations should be signed by all the authors in the order in which they are mentioned in the original manuscript also **Ethical clearance is to be submitted**.

- **Manuscript in Vancouver style in MS Word.**
- **Original/ Review article:**
  Max 2200 words, 3 Figures, 4 Tables, 20 References, Ethical Clearance is to be submitted
- **Case report/ Current topics:**
  Max 800 words, 2 Figures, 1 Table, 10 References.
- **Letter to the Editor: 500 words**
- **Abstract:**
  Max 250 words, Keywords – 4-5 words, Take Home Message – Max 50 words.
- **Title Page:**
  Title of the article, Name (s) of the Author (s), Qualification, Designation, Institution, Postal Address, Email, Mobile Number & Digital Signature
- **Declaration:**
  Article is not published/ submitted in any other journal.

— Hony Editor
JIMA, 53, Sir Nilratan Sirkar Sarani (Creek Row), Kolkata-700014
Phone : (033) 2237-8092, E-mail : jima1930@rediffmail.com
Editorial Office No.: (033) 2237-8092/ (+91) 9477493027
Website: https://onlinejima.com

[1]International Committee of Medical Journal Editors—Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *JAMA* 1997; **277:** 927-34.

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION :
Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phone : (033) 2237- 8092, Mobile : +919477493027; E-mail : jima1930@rediffmail.com
Website : https://onlinejima.com ; www.ima-india.org/ejima
Head office : Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones : +91-11-2337 0009, 2337 8680, Email : hsg@ima-india.org : Website : www.ima-india.org

Registration No. KOL RMS / 476 / 2020 - 2022

RNI Regd. No. 2557/1957
Vol. 65, No, 1, January 2021, Kolkata

Date of Publication : 20th January 2021

INDIAN MEDICAL ASSOCIATION

HEADQUARTERS, NEW DELHI

BE A ROLE MODEL

VACCINATE

DR. J.A. JAYALAL
NATIONAL PRESIDENT

DR. JAYESH M. LELE
HONY. SECRETARY GENERAL

If not delivered please return to
Journal of the IMA (JIMA)
53, Sir Nilratan Sarkar Sarani,
(Creek Row), Kolkata - 700014

Printed and Published by **Dr Sanjoy Banerjee** on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata - 700009 and Published from Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014, Editor : **Dr Jyotirmoy Pal**