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DOCTORS' DAY

Why it is Important to us....

Dr. Sanjoy Banerjee
Hony Secretary, JIMA

'Doctor's Day', is celebrated in India on July 1 every year, holds special significance for medical practitioners in India. Just like Mothers' Day we pay tribute to our Mothers, Fathers' Day to our Fathers, Teachers' Day to our teachers, Children's Day to children; it is on this day that Doctors are felicitated for their irreplaceable roles that they play in our lives. From dentists to neurosurgeons, homeopaths to heart specialists, physicians to pediatricians, Doctors' Day is the time to pay tribute to the entire medical profession. This is in commemoration of the Birth & Death Anniversary of Eminent Physician and Patriot Dr. Bidhan Chandra Roy.

The history of this special day dates back to the 1800's when an American, Dr. Crawford W. Long became the first physician to use anesthesia in an operation that he performed on March 30, 1842. To commemorate this unprecedented event, March 30 was declared as National Doctors' Day in the United States.

The red carnation was chosen as the official symbol of Doctors' Day because of the colour of the flower denotes love, charity, sacrifice, bravery and courage, all of which are synonymous with the medical profession.

Interestingly, the story of Doctor's Day in India is quite different and few people actually know why it is celebrated. First of July happens to be the Birth & Death Anniversary of a famous Indian physician, Dr. Bidhan Chandra Roy who was born on this day in the year 1882, in Patna, Bihar. After his medical graduation at Calcutta, he completed his MRCP and FRCS at London and returned to India in 1911. His career as a physician began in 1911, after he returned to India. Thereafter, he joined the Calcutta Medical College as a teaching staff, then moved to Campbell Medical School (now known as NRS Medical College & Hospitals) after which he moved to the Carmichael Medical College (now known as RG Kar Medical College & Hospitals). He excelled not only as a physician and educationist but even as a freedom fighter, joining Mahatma Gandhi in the Civil Disobedience Movement. He was instrumental in starting many institutions including hospitals and for caring for thousands of patients. Dr Roy's dedication to the upliftment of Indian society and his love for serving the people led him to the political arena, where he first became leader of Indian National Congress and later Chief Minister of West Bengal. After a life of work and service, the Doctor passed away on July 1, 1962, on his birthday.

Doctors' Day thus pays tribute to all doctors like Dr. Bidhan Chandra Roy, who spend their lives helping others. The nation had honoured Dr. Roy with Bharat Ratna and instituted Dr. B.C.Roy National Award in 1976.

Majority people are of the opinion that Doctors' Day is the Birth & Death Anniversary of Dr. Bidhan Chandra Roy and it is observed in many places paying homage to the legendary figure.

Contd.....

It was Indian Medical Association, Kidderpore Branch, Calcutta who first came out with the proposal of “Doctors' Day” in the year 1989 with Dr. Santanu Banerjee (President) and Dr. Pradip Kumar Chatterjee (Secretary) and designated 1 July in commemoration of the Birth & Death Anniversary of Eminent Physician and Patriot Dr. Bidhan Chandra Roy, which was passed first in State Working Committee, IMA Bengal State Branch and then in Bengal State Council Meeting in 1989 with Prof. Ashok Chaudhuri (State President) and Dr. Subir Gangopadhyay (State Secretary) and forwarded to IMA Central Working Committee and passed in CWC meeting 24-25 April 1991 under the then National President Dr. Ram Janam Singh (Bihar). IMA Hqrs. directed all its branches to observe 1 July as “Doctors' Day” from 1 July 1991. The IMA Hqrs. then persuaded the Government of India and after a long process ultimately “National Doctors' Day” got official recognition in India only in the year 1991 by Dept. of Health & Family Welfare, Government of India, 29 years after the death of Dr. Bidhan Chandra Roy. Dept. of Health & Family Welfare, Government of India instructed all State Governments to organize & observe 'National Doctors' Day' and 1 July 1992 became the most important date for Doctors all over India when “National Doctors' Day' was observed for the first time with Government extending financial support to IMA.

This special day is an ideal opportunity to remind people of the critical role doctors' play in our lives. Being a doctor is not just a 'job'; it is a challenging commitment to service that requires high levels of skill and precision. To make a tough job even tougher, doctors also have to deal with the reality that even a small professional mistake could drastically affect a patient's life. Doctors' Day is the perfect time for patients to acknowledge the high-pressured job and appreciate their Doctors' ability to comfort and heal.

Doctors' Day is also a significant day for doctors themselves as it provides them with an opportunity to revitalize and rededicate themselves to the practice of medicine. All doctors begin their professional lives with the noble ideals of serving humanity and healing those in need. Doctors' Day is thus is a time for doctors to reflect on their own careers, realize the responsibility they bear and redirect themselves onto an ethical path of healing those in need.

Unfortunately, the medical profession today is witnessing a rapidly deteriorating patient-doctor relationship, with people losing faith in their doctors. The easy availability of medical information, and misinformation, from the media and the Internet is also responsible for clouding a patient's view of their doctors' advice. Nowadays, doctors are more often the victims of criticism while their successes are overlooked. It is true that the medical profession carries a heavy responsibility with it, but people need to realize that behind the white coat and stethoscope is a normal human being and like in all other professions, doctors too need appreciation for their work and efforts.

On this Doctor's Day, make an effort to honour doctors for their skill and commitment. Single out a family doctor and show them your gratitude for the care they have provided you and your loved ones. This day provides students and those who work in hospitals, nursing homes or other medical facilities with the ideal opportunity to express their thanks to doctors for mentoring, being supportive and encouraging. Give your doctor a card, a single red rose, a gift or just say a simple, heart-felt 'Thank You': it will brighten up their day and make them feel respected and appreciated.

Wish all my colleague **“A Happy Doctors' Day” !**

Dr Rajan Sharma
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IMA

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Honorary Secretary
General, IMA

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Honorary Editor,
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Prof. (Dr.) Jyotirmoy Pal
MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Hony. Editor, JIMA

Relation of doctor with the society — A Tale of hope and despair

In Bana Parva of Mahavarata, Yaksha asked Yudhishthira 18 questions – known as **Dharma – baka Upakhanya.** Among several questions, one of them was

Yaksha : Who is the friend of one who is ill?

Yudhishthira : The physician is friend of who is ill.

"A Good Physician treats the disease; a great Physician treats the patient who has the disease"

Doctor's Day is a day which reminds us the age-old concept of Doctor-patient relationship. Doctor's Day is emotional to us being birthday of our Father of medical profession Dr B C Roy. We do not celebrate this day to show our strength and political organizational capability or to put our demands to authority. This day is rather celebrated to remind us regarding what is the expectation of the society from us and what we expect from our society. It also reminds us regarding not to deviate from the morals laid down by our father.

Doctor –patient relationship evolved over last 5000 Yrs.

Vedic Age :

Among various professions, the Physicians stand out because they are the reason of good health, happiness and ultimate survival of race. In Hindu Mythology, Vishnu is the God of Sithi (palan) and as Dhanvantari is the God of Medicine and avatar of Lord Mahavishnu - Physicians were worshiped in the Vedas. Position of Physicians were well established in period of Vedas during 5000BC. With the passage of time as civilization grew, human desires flourished in different dimensions, infatuation, ego and greed engulfed the society. The role of Physicians towards society was documented in Charak Sanhita.

Ancient Civilization :

Charaka added Physicians should be friendly towards all, having compassion for the ailing and be devoted to patients who can be cured, while accepting the inevitable in case of patients who are dying. Charaka mentioned that mere commercial spirit should not be allowed to prevail in this profession. Charaka criticized those "make merchandise of medicine" and advised "not to speak lies and backbite others". This old literature indicates deviation from high moral laid down in the Vedic period. Our great ancestors felt that to hold society i.e. medical profession under norms meant to hold string of Lattu (spinning toy). So came the Hippocratic Oath.

Hippocratic Oath (written 5th or 6th century BC) was oldest binding documents in history regarding duty of Physicians. Physicians were bound by the Oath to treat an ill with best of his ability, preserve patient's privacy and teach secrets of medicine to next generation. Actually the Greeks developed a system of medicine based on empirico-rational approach. This was a deviation of system of Vedas where doctors were worshiped while here the Doctor-patient relationship was described based on cooperation in a democratic fashion. Hippocrates, while in one hand, established code of conduct for doctors, on the other hand, he documented the Bill of rights for patients. So Doctor patient relationship was brought down from heaven to earth, which was may be need of that period.

Dark Age :

With the fall of Roman Empire, Dark Age in Europe started. Religious predominance and supernatural

power dominated the entire Europe. Magic-religious beliefs personified in old and new Testaments were revived and became widely accepted. There was a gradual deterioration, weakening and regression of doctor – patient relationship.

In the seventeenth century, the society has lesser number of Doctors and medicine was considered as right of privileged society. Treatment was mainly symptom based and Doctors was busy to please upper class patients particularly who belongs or close to Royal/Raj family.

French Evolution :

French revolution brought a renaissance in human thought and culture throughout the world. Mankind's liberalism, equality, dignity was redefined. Thus, the nature of Doctor patient relationship changed. The model that became popularised was the Guidance – cooperation model. As a result in late 18th century, the hospitals emerged to treat the underprivileged society. At this period, there was growth of microbiological knowledge and surgical skills. New system of medicine developed, based on accurate diagnosis rather than symptom based treatment. The new model required examination of patient and anatomical knowledge of human body. So, in this model, the patient was passive and doctor became dominant.

Nineteenth Century :

In this period, the doctor patient relationship had taken a new dimension. Patient was considered as a person. The patient and the doctor were allowed to develop communication relationship. So here patient was active participant in medical practice. "The patient was not simply an object but a person, needing enlightenment and reassurance" – report of planning committee of Royal college of Physicians, London.

Twentieth Century :

There was a rapid advancement of science in this century. Empathy was partially taken away by structured scientific approach of medicine. Patients were increasingly considered as substrate, although, consumerism till then was not developed until later part of this century.

Twenty-first century :

From the later part of twentieth century consumerism started to dominate. Patients were considered as customer. The concept of client prevailed in society. Commercialization of medical practice engulfed the ethics and modalities of medical practice. Rapid advancement of knowledge converted a physician to a technologist. Micro health predominated over macro health. Public health system had taken a back gear. Insurance based practice, evidence based practice, litigations, Consumer Protection Act, Physical assault on doctors, exuberant cost of medical care were the key issues in medical profession. Medical professionals were controlled by politicians, bureaucrats and industrialists – the physicians were converted to salaried professionals who were not allowed to take part in Policy making.

In the twentieth century, the famous novelist Manik Bandhyopadhyay described in his novel Putul nacher Itikatha (Story of Puppetry) - the pain of an honest doctor being a Puppet in hands of Politicians. The story depicted the transition of Doctor-society relationship from earliest twentieth century to late twentieth century.

We are in a transition phase. While on one side lies the almighty commercialization, on the other lies the morality and novelty of the profession. We are perplexed and baffled. We are not considered God. Our every action is assessed. Falling to withstand pressure of commercialization, sometimes we deviate from our Hippocratic Oath. Consumerization has thrown us into a new challenge. While on one hand, a doctor working even with the best intentions, runs the risk of getting beaten up by the public in front of camera, on the other hand there is the ever increasing legal hurdles in consumer courts, health commissions, police enquiries and criminal courts. In the developed countries, there is a clear legal difference between manslaughter and various degrees of murder but in India, there is no such difference and a doctor can be booked on murder charge merely at the words of the patient party. The media then publishes the photo of the doctor being taken to the police station and the doctor's family has to bear the brunt. Media trial starts before legal trial. For a studious doctor, who is spending his/her entire life in the pursuit of science and knowledge, this sudden face-off with police proceedings and courts shatters the entire life in one moment. Our society seems to be nonchalant to this aspect of doctor bashing and even in the times of the COVID-19 pandemic, attacks on doctors were reported frequently all over the country. Last year, a respected

elderly gynecologist was slapped in front of camera in a Calcutta hospital. But the subsequent reaction of the media and the public were ostensibly in favor of the perpetrators and a famous newspaper even commented that doctors have to be ready to face such reactions from the patient party. In a highly comedic reaction, the scene from one of Satyajit Ray's movie, "Aparajito" was invoked to justify doctor bashing by the patient party!!

Depiction of the medical profession in art and literature in India :

Art and literature in all forms have significant effect on the collective psyche of the masses. In Nazi Germany, continuous propaganda against the Jews helped to shape the public hatred against this community and led to one of the most heinous crimes against humanity. In India, over the last 5 or 10 years, a section of the media and the intelligentsia are propagating a very negative, subversive view of the medical community.

However, we think that this animosity towards doctors is not something new. This has a long tradition in India. Bonoful was a famous physician-author in Bengal. He had written many novels on the life of doctors like "Trinokhondo", "Nirmok", "Agniswar", "Erao Ache" and "Hatebajare". In these novels, the life of doctors in the first part of the twentieth century is depicted in vivid details. Since he was a physician, he had the eyes to see the jeopardies in the life of a doctor. He has written about the threats given to doctors by the patient party in villages, the numerous attempts at character assassination (one can remember a similar recent incident in Calcutta) and the frustration of doctors at the stupidity and banality of the public. This tradition of alienating doctors in the Indian society is a part of the larger trend of suspecting anything new or scientific. In the modern era of social media, this hate and anger have reached new heights. During the demonetization of India in 2016, there were numerous Facebook posts about "hidden treasure" of doctors and how they were burning their "black money". Many doctors were trolled online by name.

"Kaalbela" a famous novel in Bengali, by Samaresh Majumdar stated a lot of disparaging remarks about the medical profession. One examples are given below:

"কলকাতা শহরের মানুষের রোগ বোধহয় লেগেই থাকে। এবং এতে ডাক্তাররা খুশিই হন। .... যদি আজ এদের সবাই সুস্থ থাকতেন তাহলে ডাক্তারের মন কেমন থাকত? অর্থের জন্য মানুষের মন সবসময় নিম্নগামী হয়।"

(Perhaps people in Calcutta suffer a lot from diseases. And doctors are pleased with this. ..if everyone is healthy today, would the doctor be happy?Greed for money makes them small-minded. This was written at a time when Indian doctors were actively trying to develop primary health care in remote villages.

Popular songwriter of Bengal, Nachiketa Chakraborty, once wrote a highly insulting song about the medical profession. Some lyrics from that song are quoted here to make our readers realize the level of hatred among artists in Bengal about our profession.

কসাই আর ডাক্তার একই তো নয়
কিন্তু দুটোই আজ প্রফেশান
কসাই জবাই করে প্রকাশ্য দিবালোকে
তোমার আছে ক্লিনিক আর চেম্বার

(Butcher and doctors are similar. Butchers kill animals in the open; doctors do it in clinics and chambers.)

রোগীরা তো রোগী নয় খদ্দের এখন
খদ্দের পাঠালেই কমিশান
ক্লিনিক আর ডাক্তার কী টুপি পড়াচ্ছে
বুঝছে না গর্দভ জনগণ

(Doctors now consider patients as customers. They take commission for sending customers to labs. Our public is too naïve to understand how clinics and doctors are swindling them.)

Interestingly, in spite of such egregious comments about a particular profession, Nachiketa was never held accountable for his scandalous lyrics. He enjoyed a certain degree of adulation in the media and he

performed this hate song in numerous concerts to rousing applause.

The Hindi film industry (Bollywood) is the most influential art industry in India. Whether we like it or not, Bollywood films influence a lot of people in India and shape the majority public opinion.

The 1982 film, **Bemisaal,** is centered on the life of two doctors, played by Amitabh Bachchan and Vinod Mehra. The character portrayed by Mehra is shown to be an unscrupulous doctor who wants to attain success by "hook or crook". For this, he is shown to do unethical work for money.

In the film, **Andhadhun,** midway in the movie, there is sudden appearance of a "Dr Swami" who operates an organ trafficking ring from a peculiar dark house, with the help of two servants only. The doctor's character is shown to be a ruthless opportunist who talks about cutting out organs from a healthy person for profit.

The 2013 Bollywood flick, Ankur Arora Murder case, is a nasty depiction of the medical profession. Kay Kay Menon portrays a senior surgeon who is shown to be rude and business oriented. His character depiction is quite unrealistic and designed to generate hatred against doctors in the hearts of the audience.

The daily newspapers of India are usually full of anti-doctor articles. Of course, there are a few favorable articles on doctors in the media. But art is mostly anti-doctor. As such, there are a very few Indian novels or movies where doctors or people of science are given the lead characters. This is in sharp contrast to the western World where there are numerous creations on the life of doctors like "House MD", "Grey's Anatomy", "E.R." and "Cardiac Arrest". These art forms have a lot of positive aspects about the life of medical professionals. But in India, except a few obscure movies like "Anand" or "Ek Doctor ki Maut" or "Ganashatru", there are almost no depictions of our life in the art world. If suppose an alien comes to this earth and watches Bollywood movies, it will think that India is full of people who sing and dance and fight villains on the streets with no person of science in the country.

The history of the human civilization has repeatedly proven that when a group is oppressed, it has to stand up for itself as no one else will defend it. This was true for the repressed African Americans, for the jews in nazi Europe and for the modern Israel. So, doctors in India have to stand up for themselves if they want to make their lives better.

Our role in Pandemic :

Yes ,Our Doctors shown their brave faces during current Pandemic. Taking risk of his own life taken challenges and more than 100 doctors sacrificed life as Martyrs in COVID –WAR. During Lockdown period when all are confined in home , only Doctors and Police Personals were in Street. Wheather they got adequate protective devices , wheather got adequate food, rest , remuneration – no doctor denied duty , rather jumped to rescue mankind. Definitely it was recognized by Government both Central and State – thankful to them. But inspite of giving such service there are several incidence of harasement of Health care workers in society presuming they are spreader of infection, that I pointed out in my previous editorial " Untouchability".

Our Introspection :

But we also need some introspections. We need to think that whether we deviated from the pathway shown by Legends like Dr B C Roy, Dr Nilratan Sirkar, Dr Jibraj Mehata , or we engulfed the poison of consumerism, or we have surrendered to pressure of commercial houses.

"If you want peace of mind, do not find fault with others . Rather learn to see your own faults"
— Maa Sarada

In my last editorial I described untouchability in context to society and doctors who are treating contagious diseases. But in other window we see practice of untouchability which is considered as a status symbol by a group of physicians. Here untouchability means keeping distance from doctors, not partnering his sorrows, not being his moral brother, sister, mother or father. Our doctors prefer not to respond to phone calls, not to wish during morning walks, not to attend funerals, not to attend patients apart from scheduled consultation hours. One day I visited a town near my city Kolkata in one ceremony, i asked about my friend who is endocrinologist practising in the town. The man replied that we know him, he could be some specialist, but we do not consider him a good Doctor. On asking the reason behind it, the person cited that when his father had died, he had called him up for a death certificate,

however since he was an endocrinologist, he didn't issue one. Doctor replied " I am specialist in Diabetes, go to General Doctor ". He continued saying that his father-in-law was great, citing an incident in which his grandfather was suffering from diarrhoea, and his father in law treated him the whole night sitting in their room wearing a loongi. This is a story how perception of Physicians changed in society in last 5000 yrs – From God to saviour, from saviour to friend and philosopher, from friend to service providers. We know there is vandalism, there is a prevailing myth that doctors are spreaders of infectious diseases. In London, during Cholera epidemic – popular belief were patients are taken in quarantine to lean anatomy by dissecting dead body. We know this is wrong practice in part of society, but this happened due to diminished social acceptance of a Doctor in his locality , who prefers to practice outside his neighbourhood for not to be disturbed in odd hours in residence.

Doctors and Pharmaceutical industries having an unholy relation is a whispering rumour in society. I have no proof how many doctors have really taken bribes or not and if so how much. However, I firmly believe it is also our responsibility to curb such a perception prevailing in our society, also from minds of our patients by our act. Some say physicians should prescribe generic brand only or cheapest brand only to build up confidence among our patients. However, I disagree – it is not the question of cheaper or costlier medicine or question of minimum investigations or huge investigations, it is our approach that builds up confidence in our patients about our integrity and credibility. It is the sixth sense that a patient have to smell our motive. We can prescribe a molecule being motivated by some Pharma industry, but most importantly we have to convince ourselves whatever we do, that is for the best interest of patients and for nobody else. If it happens otherwise, our patients will lose faith in our prescriptions. If patients lose faith, regulators and lawyers will come forward to fill up the gaps.

It is just for awakening introspections, not to hurt anybody.

Our Oath in Doctors' Day :

Doctor's day is auspicious to our fraternity. The life of Dr B C Roy is a story to Physicians. We should give ourselves opportunity to look into our own act , to have a trial inside us , to pull back from a slide of hill.

He is torchbearer to our profession. Take an oath to re-establish relation of doctor and patient in society – not to a extent of God, but to prove "i am your man".

Except for a few black ships, we are dedicated to the society. It is the doctors who are sacrificing their lives in COVID battle. We are always in the battlefield, taking chances of our own lives. So why is there so much suffering, so much criticism from society. The answer lies in a conversation of Thakur Sri Ramkrishna Dev and Swami Vivekananda.

Swami Vivekananda : **Why do good people always suffer ?**

Sri Ramkrishna : **Diamond cannot be polished without applying friction . Gold cannot be purified without putting into fire. Good people always go through trials and hardships.**

Medical Profession is a Golden Profession. Whatever be the hurdle profession will gliter.

So Call of Swami Vivekananda is relevant to our Medical Professionals in these odd days

"ARISE , AWAKE AND STOP NOT TILL THE GOAL IS REACHED"

JAI HIND BANDEMATARAM JAIBHARAT

Review Article

RDW & RBC Histogram — All that Physicians should Know & Apply in Clinical Practice

Sudhir Mehta[1], Shaurya Mehta[2], Prabhav Bhansaly[3]

Traditionally, anemias have been classified on the basis of blood indices (MCV, MCH, and MCHC) and reticulocyte count (reticulocyte production index- RPI). This traditional classification has enjoyed long innings with pathologists and hematologists. Newer automated blood cell analyzers provide an index of red cell volume distribution width (RDW) or heterogeneity and a histogram display of red cell volume distribution. This write- up on classification of anemias based on mean corpuscular volume (MCV) and heterogeneity (RDW) will help clinicians in the initial classification of anemias based on the print-out of automated counters. Also, this new classification obviates the use of reticulocyte count in the initial categorization of anemias. Understanding of RDW & RBC histogram is useful not only in diagnosing early deficiency states when RBC indices are normal but also, in following these patients after treatment, whether the response is physiological or pathological.

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Key words **: Cell counter, RBC histogram, RDW, MCV.**

The present-day classification of anemia is dependent on values of blood indices (MCV, MCH, and MCHC) and the corrected reticulocyte count (reticulocyte production index-RPI)[1,2]. The change from chamber counts to flow cytometry for routine blood counts has brought not only improved speed and precision, but also new measurements permitted by the analysis of large numbers of single-cell measurements. The distribution of red cell volume now is displayed in histogram form[3]. Measured as coefficient of variation (CV) and reported as red cell distribution width (RDW), the heterogeneity of distribution of red cell size (the equivalent of "anisocytosis" in analysis of peripheral blood smear) now forms part of the reported automated blood count. The present article highlights the fact that using the data generated from the automated hematology analyzers in terms of MCV and RDW, the anemias can be re-classified without the consideration of RPI and how the classification based on the mean and heterogeneity of red cell size is more physiologic.

Before discussing this new classification, a basic knowledge of RBC histogram and its components is put forth for better understanding.

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Editor's Comment :

RDW has

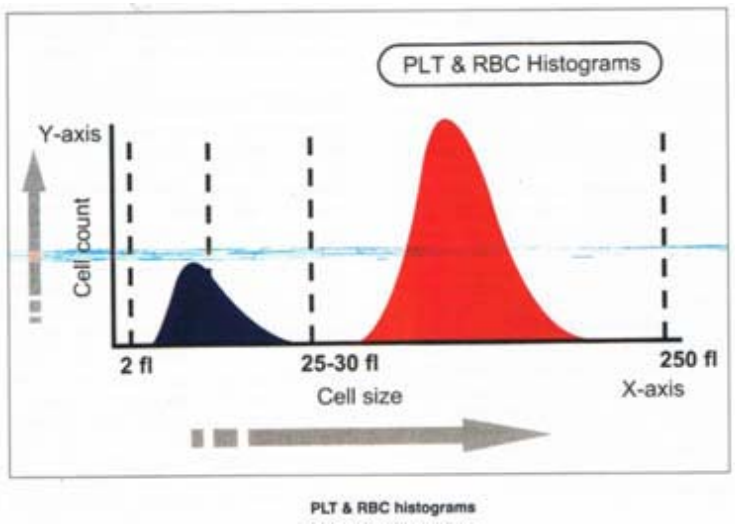
- **added new dimension to the understanding of RBCs**
- **given more meaningful clinical classification of anemias**
- **given a bedside parameter to make prompt clinical diagnosis of anemia**
- **great importance in detection of early iron deficiency & megaloblastic anemias when RBC indices are normal**

Histogram :

Hematology histogram is a graphic representation of different blood cell types. Hematology analyzers count and size thousands of cells to produce a histogram. A histogram is displayed by plotting the number of cells on the y-axis. The cell size in fl is displayed on the x-axis.

Red Cell Histogram :

A hematology analyzer aspirates the blood sample, measures, dilutes and feeds it into the transducer chamber. During each analysis, analyzer's pneumatic system creates a vacuum and blood cells passes through the aperture on one end of the transducer chamber. This causes change in the resistance of the conductive diluent. RBC and platelets are counted simultaneously in the same channel. Particles falling between 2fl and 30 fl are grouped together as platelets, while particles larger than 40 fl are counted as red cells (Fig 1).



PLT & RBC histograms

Fig 1

The RBC histogram has various components (Fig 2). The MCV is calculated by drawing a perpendicular from the peak to the baseline. The point where it intersects is the MCV. RBC abnormal distribution flags appear when the RBC histogram shape, width or position exceeds certain limits. In this situation, the smear should be scanned for abnormal RBC morphology such as anisocytosis, poikilocytosis, RBC agglutination, fragmented RBCs, rouleaux formation, multiple RBC populations (following blood transfusion). A RBC histogram may show double or multiple peaks in dimorphic anemia, following blood transfusion, sideroblastic anemia or when there is marked reticulocytosis.

When MCV is very low (<55fl), RBC histogram may merge with platelet histogram. In this situation, both RBC and platelet counts will be inaccurate.

Factors producing falsely high RBC count include presence of large platelets, marked thrombocytosis and fragmented red cells. Falsely low RBC count is generated in presence of cold agglutinins, EDTA-dependent agglutination or RBC lysis due to mishandling.

Falsely high MCV is produced by red cell agglutination, excess EDTA, EDTA-dependent agglutination or samples stored at room temperature.

Falsely low MCV is produced by hypochromic RBC, severe anemia associated with marked thrombocytosis and increase in ambient temperature.

The red cell distribution width (RDW) is a measure of anisocytosis i.e. this value indicates the degree of red cell size variation or how much difference exists between the largest and smallest red cells. This value is derived from the MCV histogram. An increased RDW corresponds with an increase in anisocytosis on the peripheral smear. The RDW is reported in two ways. The RDW-SD measured in fl is determined by measuring the actual distribution width of the RBC population at 20% above the baseline. The RDW-CV is the coefficient of variation based on the standard deviation of the distribution width divided by the MCV. The RDW is only available if it is included in the instrument menu. Although different manufacturers use slightly different methods of obtaining data, the RDW is generally thought of as the coefficient of variation of red cell volume distribution.

RDW-CV = (standard deviation of RBC volume / mean MCV) X 100

1 SD reflects the size variation of the erythrocytes round the mean. As the 1 SD is divided by the MCV, the RDW-CV also depends on the mean size (MCV) of the erythrocytes. RDW-CV is sensitive to pick small RBCs (microcytes) in the blood.

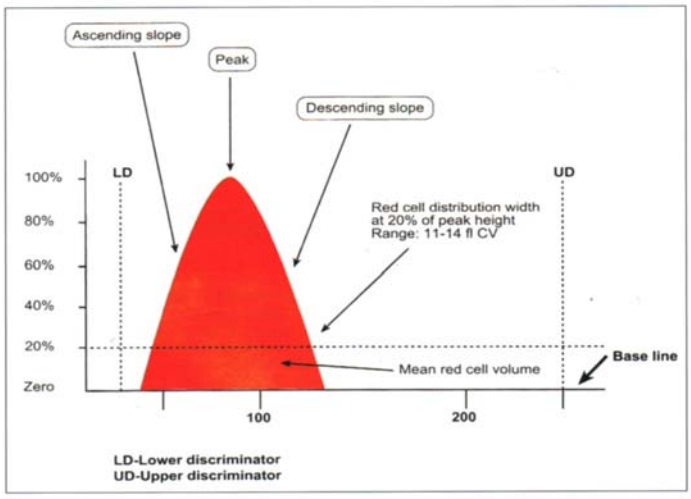
Reference values: 11.5-14.5%

RDW-SD is the actual measurement of the width of the erythrocyte distribution curve. This measurement is performed at a relative height of 20% above the baseline. RDW-SD is more sensitive to pick large RBCs (macrocytes).

Reference values: 35-45 fL.

The RDW, coupled with the MCV, gives more relevant information than an individual index. The following is an attempt to clarify the relationship of the MCV and RDW.

1. Red cells that are all microcytic or macrocytic will have a RDW in the reference range



Components of RBC histogram

Fig 2

and a decreased or an increased MCV.

2. Red cells that vary in size and have an average size within the reference range will have an increased RDW and a normal MCV.

3. Red cells that vary in size and have an average size below or above the reference range will have an abnormal MCV and RDW.

In essence, RDW in conjunction with MCV can provide a means to reclassify anemias (Tables 1,2,3). Also, it is worth mentioning that no erythrocyte disorder can have low RDW. Low RDW is not observed normally but theoretically, it is possible only at marrow level when RBC produced by marrow have less heterogeneity than the accepted normal. Low RDW with low MCV is quoted in thalassemia minor and likewise, low RDW with high MCV in aplastic anemia. But in general, both these fall under normal RDW.

Discussion

The initial classification of anemia can be improved substantially by including RDW and histograms of red cell volume as these variables have become part of automated hemogram. Because the MCHC varies little except in severe iron deficiency, the terms "hypochromic" and "normochromic" parallel low or normal MCV and therefore are redundant[4]. Use of MCV and RDW suggests the new terms of homogeneous microcytic (normal RDW, low MCV), heterogeneous microcytic (high RDW, low MCV) and so forth (Tables 1,2,3).

Nutritional deficiency, whether of iron, folate or vitamin B12, always causes increased red cell volume heterogeneity. While these patients are anemic on the average, even those who are not anemic have high RDW. As the nutritional deficiency progresses, more abnormal cells are produced and admixed in the peripheral blood[5]. In early or mixed nutritional deficiency, RDW is high while MCV remains within the normal range; heterogeneous normocytic indices then are the earliest clue.

In contrast, normal RDW accompanies pure hypoproliferative anemia resulting from chronic disease, marrow toxicity or aplasia, independent of the MCV; homogeneous micro-, normo-, macrocytic anemia. Thus, early iron deficiency is heterogeneous normocytic in contrast to chronic disease, which is homogeneous normocytic; more advanced iron deficiency is heterogeneous microcytic, in contrast to thalassemia minor, which is homogeneous microcytic. Patients with long standing aplastic anemia have high MCV unless they have been transfused. Since the RDW is normal, such aplastic states are associated with a homogeneous macrocytic anemia in contrast to patients with folate or vitamin B12 deficiency (heterogeneous macrocytic)[6].

Table 1 — Classification of microcytic anemias on basis of RDW

MCV low & RDW normal (microcytic homogeneous)	MCV low & RDW high (microcytic heterogeneous)
Alpha thalassemia minor	Iron deficiency
Beta thalassemia minor	HbS-beta thalassemia
Hb E trait	Homozygous Hb E
	Anemia of chronic disease
	Severe thalassemia- HbH disease, Hb E/beta thalassemia, homozygous beta thalassemia
	Red cell fragmentation

Table 2 — Classification of normocytic anemias on basis of RDW

MCV normal & RDW normal (normocytic homogeneous)	MCV normal & RDW high (normocytic heterogeneous)
Normal	Early iron deficiency
Chronic liver disease	Microangiopathic hemolytic anemia
Hb S & C trait	Hereditary spherocytosis with spleen
Transfusion	Myelofibrosis
Acute bleeding	Hb SS disease
Hereditary spherocytosis without spleen	Hb SC disease
Chemotherapy	Anemia of cancer- acute leukemia, solid tumors
CLL, CML	

Table 3 — Classification of macrocytic anemias on basis of RDW

MCV high & RDW normal (macrocytic homogeneous)	MCV high & RDW high (macrocytic heterogeneous)
Aplastic anemia	Normal newborn infants
Preleukemia	Folate deficiency
	Vitamin B12 deficiency
	Immune hemolytic anemia
	Hemolytic disease of newborn
	Aplastic anemia in remission
	Cold agglutinins
	Acute leukemia (on treatment & post-BMT)

Among the hereditary hemoglobinopathies, there is a direct relation between anemia and heterogeneity[5]. Hemoglobin S or C trait is associated with a normal RDW unless there is concomitant iron or folate deficiency[7]. While heterozygous thalassemia generally is associated with normal hemoglobin and RDW, when there is slight anemia associated with thalassemia, RDW will be increased slightly. Likewise, in hemolytic disorders, "shift" reticulocytosis and therefore an increased MCV is proportional to the duration and degree of anemia[8]. When reticulocytosis is due to transient blood loss or hemolysis or to compensated hemolytic anemia, reticulocytes are only

5-8% larger than and nearly as heterogeneous as the cells into which they mature and the MCV and RDW are normal. Therefore, in increased red cell destruction from any cause and with any MCV, nonanemic compensated disorders are homogeneous; in contrast, anemic disorders are heterogeneous.

Chronic lymphocytic leukemia, cold agglutinin disease and RBC fragmentation all have artifactually abnormal MCV and RDW because flowcytometry technology defines red cells by volume thresholds instead of hemoglobin pigmentation. Any cell 36-360 fl will be counted as a red cell; any spurious cell that is >1% as numerous as the red cells will influence the reported values.

Case-based Discussion :

Case 1 : A 50 years old man presented in Medicine OPD with shortness of breath. On examination he had marked pallor. An automatic haematology analyser revealed Hb of 6.8gm/dL, MCV of 53.3 fL with RBC histogram peaking to left, high RDW-CV and normal WBC and Platelet histograms.

Case 2 : A 20 years old primigravida presented in antenatal OPD for routine checkup. CBC by haematology analyser revealed Hb of 11.5gm/dL, total RBC of 6.55 million/uL, MCV of 58.2 fL and RDW 25.6 suggestive of homogenous population of RBCs.

Case 3 : A 18 years old pure vegetarian male presented to medicine OPD with mild icterus and easy fatigability. On examination he had mild pallor. Blood analysis showed Hb of 8.2 gm/dL, MCV of 113.4 fL and RDW of 119.4 fL with shift of RBC histogram to right.

Case 4 : A 12 years old boy presented with marked pallor, purpura and fever. Complete blood count revealed pancytopenia. RBC histogram skewed to right, RDW was normal. WBC histogram shows lymphocyte peak and faint neutrophil dome. Platelet histogram has abnormal distribution and descending slope not touching baseline.

Case 5 : A 55 years old male presented with icterus and occasional hematuria. Complete blood count revealed Hb of 11.2gm/dL, total RBC count of 2.24 million/µL, MCV of 98.2fL, Hct-22%, MCH 50 and MCHC 50.9.

Now a detailed study of the cases :

Case 1 : Iron Deficiency Anaemia (IDA)

A low MCV with high RDW (i.e anisocytosis) suggests iron deficiency anaemia (Table 1). The RBC histogram is broad with most cells in the microcytic area. IDA was confirmed by Iron studies & presence of occult blood in the stool.

Case 2 : ß-thalassemia minor.

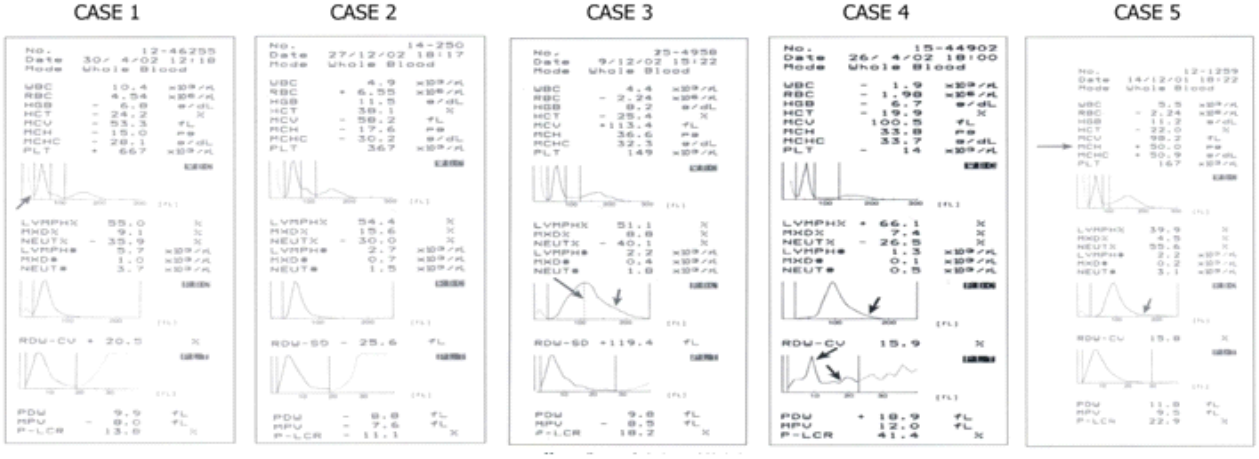
Low MCV with normal RDW suggests heterozygous hemoglobinopathy like ß-thalassemia (Table 1). RBC histogram shows a microcytic peak with narrow base as the cells shows very little size variations. Hb is normal but TRBC is disproportionately high as compared to low MCV 58.2. PBF examination revealed uniformly sized RBCS (homogenous RBCs, normal RDW). Hb Electrophoresis by HPLC revealed high HbA2 suggestive of Beta-thalassemia trait.

Case 3 : Megaloblastic Anaemia.

In this case, MCV is high with increased RDW (heterogenous RBCs) suggestive of most common cause i.e. megaloblastic anemia (Table 3). RBC histogram has shifted to the right with large population of RBCs seen in 150-200 fl range. Diagnosis is confirmed by estimating serum Vitamin B12 & RBC Folic acid.

Case 4 : Aplastic Anaemia

Pancytopenia with macrocytic anemia, normal RDW is suggestive of aplastic anaemia (Table 3) which was later confirmed on bone marrow biopsy. WBC histogram revealed predominant lymphocytic



population with scanty neutrophils.

Case 5 : AIHA with cold agglutinins

Complete blood count shows mild macrocytosis (MCV-98.2fl) with disproportionately low TRBC & haematocrit with high MCH, MCHC. RBC histogram revealed a descending slope extended to right. In this case agglutinated RBCs produced a lower RBC count resulting in spuriously high MCH & MCHC.

Role of RDW In Diagnosis of Early Iron Deficiency & Its Follow-up (Fig 3)

In early iron deficiency state when Hb & RBC indices are apparently normal, RDW is the ONLY parameter to be deranged which is reflected in unimodal but slightly widened RBC histogram. At this stage, RDW is the only parameter which differentiates from normal state.

In frank IDA, changes in RDW & RBC histogram are very much apparent as discussed in Case 1.

When IDA is treated with parenteral Iron therapy, TRBC start increasing but MCV takes more time to normalize. Two populations of RBCS- pre-existing microcytes & newly formed normocytes exist which can be easily seen on RBC histogram but not so much clear on PBF. This type of normocytic response is physiological.

In another situation, MCV normalizes earlier but there are two populations of RBCS- microcytes & macrocytes, which manifest as bimodal RBC histogram as seen in Fig 3. This type of macrocytic recovery is apparent only on RBC histogram and is suggestive of unmasking of megaloblastic anemia due to Vit B12 /Folate deficiency. Realising this fact is useful in IDA patients in whom Hb starts falling after initial rise.

Role of RDW in Diagnosis of Early Megaloblastic Anemia & Its Follow-up (Fig 4)

Like in IDA, early megaloblastic changes manifest as change in RDW-SD before there are changes in RBC indices. At this stage, HB is normal & PBF does not reveal apparent anisocytosis.

In frank MA, changes in RDW & RBC histogram are very much apparent and diagnosis can be easily made.

When MA is treated, there can be either normocytic or microcytic response. The latter type of microcytic response is pathological and is suggestive of unmasking of iron deficiency anemia.

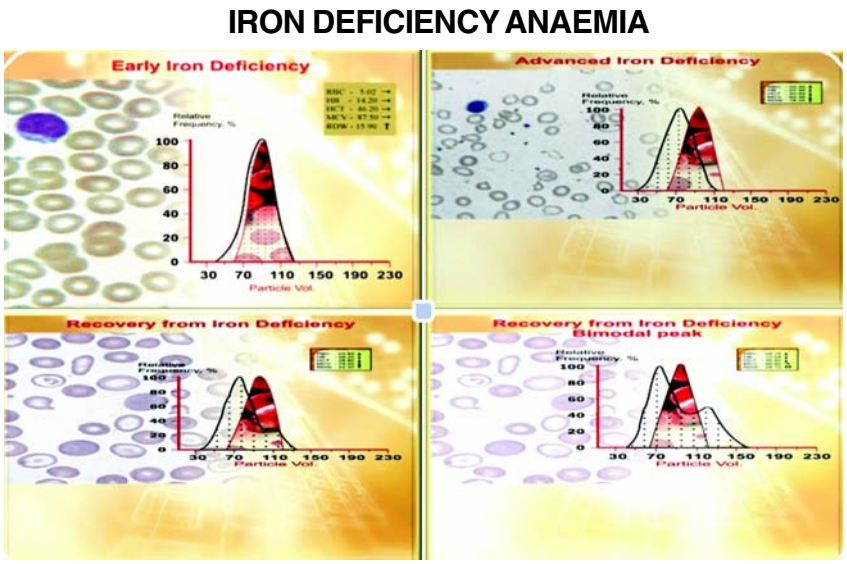


Fig 3

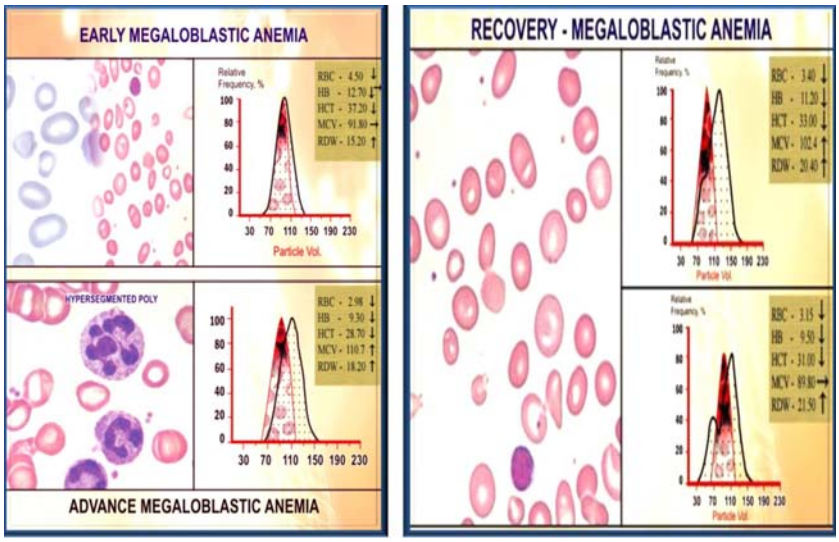


Fig 4

Conclusion

The six categories described in Tables 1, 2, 3 yield a short, fast and accurate differential diagnosis from the initial blood count (MCV and RDW) generated by automated hematology analyzer and suggest the more physiologic basis for classifying the anemias. Combining the older and newer classifications, anemias can be grossly summarized as:

- Hypoproliferative disorders- independent of MCV,

have normal heterogeneity/ homogeneity (normal RDW).

- Nutritional Disorders- independent of MCV, have increased heterogeneity (raised RDW).
- Hemolytic Disorders- independent of MCV, have heterogeneity that is increased in direct proportion to the degree of anemia.

Understanding of RDW & RBC histogram is useful not only in diagnosing early deficiency states when RBC indices are normal but also, in following these patients after treatment, whether the response is physiological or pathological.

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Review Article

Transgender Medicine for the General Practitioner

Suja Sukumar[1], Sanjay Kalra[2]

In the recent years more transgender patients are seeking medical care for gender affirmation. Physicians often perceive transgender health care as hopelessly enigmatic. For a primary care physician to provide transgender health care, he/she should know the basics of transgender health, be able to use appropriate language and properly interact, understand cross sex hormone therapy, and the risks and adverse effects associated with it. The aim of this article is to enable primary care physicians to provide basic transgender care. We discuss basic terminology; a few interactive tips; and transgender specific care which includes not only the hormonal and surgical treatment but also their reproductive, metabolic, osteocrine and social health.

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Key words **: Communication, Gender reassignment, Transgender health, Trans feminine, Trans masculine.**

The transgender community is an important, and integral part of Indian society. According to the Indian Census 2011, there are 490000 transgender individuals in the country[1]. The Government of India has introduced progressive legislation (The Transgender Persons (Protection of Rights) Act, 2019) to ensure that they get their due legal rights[2]. This review is an effort to help these members of society to achieve similar rights in health as well.

Health providers often perceive transgender health care as hopelessly enigmatic. They are often scared that they would offend the patients by using the wrong language or feel they are poorly trained and prepared for the care of transgender patients. We have discussed a few interactive tips for transgender specific care.

Communication :

Communication with transgender patients should be done in a respectful and sensitive manner[3]. Ensure privacy while asking sensitive questions. It is possible that accompanying people may not be aware of a patient's medical, gender and sexuality status. Address patients using their preferred pronouns (masculine or feminine). The name on the records may be in congruent with their appearance. Resist the urge to assume the gender identity and sexual orientation of an individual before you. If you are not sure always respectfully ask how they would like to be addressed. If you address them wrongly don't hesitate to apologize. Do not mention their assigned name at birth as the 'real name', they consider this as a dead name and by asking for real name you imply that their current gender identity is fake.

Editor's Comment :

- **Transgender community members do not get adequate attention at the primary health care level.**
- **One must communicate with them in a sensitive, empathic and respectful manner.**
- **Psychosocial health, legal issues and social modulation must be kept in mind.**
- **Infection prevention, cancer screening, dermatologic conditions and metabolic risk reduction must be addressed.**
- **Optimal care for gender affirmation, osteocrine health, contraception/fertility must be offered.**

Use politically and culturally acceptable words and euphemisms to discuss transgender and sexuality. Ensure that health records reflect a person's chosen gender. Electronic medical records may need to be modified to allow non-binary/third gender descriptions.

These communication skills and sensitivity should be exhibited not only by doctors, but by all health care professionals (Tables 1 & 2). Train your staff to use respectful language and behaviour. Personal biases, religious beliefs, likes and dislikes should not be allowed to interfere with the quality of health care received by any patients. Treat them with respect and courtesy you would like yourselves to be treated with.

Transgender-specific Care

The first and foremost of a health care professional is to do one's homework and learn about the transgender community[4]. Understand that being LGBTQ (lesbian, gay, bisexual, transsexual, queer) is not a choice or disease. Moreover, their medical

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Table 1 — Attributes of a Transgender-friendly Health Care Professional

- Acceptance of each individual's wishes and preferences
- Empathy in words and action
- Inclusive behaviour in health care
- Openness in discussion of person-significant issues
- Up to date provision of health care

Table 2 — The Cardinal Rule for Transgender Care

- Privacy in clinical conversation
- Partnership in decision making
- Provision of appropriate clinical services
- Proper guidance regarding health care
- Proactive support in psychosocial legal care

therapies are not cosmetic, they are life changing and lifesaving. Every ailment that a transgender person get is not due to hormone replacement therapy. They are normal people who can get sick like other normal people.

"Transgender" is an umbrella term that describes people whose gender identity or expression does not match the sex they were assigned at birth. For example, a trans woman may identify as a woman despite having been born with male genitalia, male gonads and male chromosome. Cis gender refers to people whose sex assignment at birth corresponds to their gender identity and expression.Gender dysphoria refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's assigned gender at birth.

Apart from routine medical and metabolic screening, the following issues need attention in certain transgender individuals.

History Taking :

History taking should be carried out in a sensitive manner, ensuring privacy. The hierarchy of questioning should be more from non-threatening to threatening questions, from medical to endocrine challenges, from non-genital to genital issues from non-sexual to sexual topics, and from sexual thoughts and fantasies to actual experiences[5].

Both a medical and a psychological history must be enquired into. Do ask about their family background and support system. Specific questions related to transgender individuals include an organ inventory and history of surgical procedures in the past[6]. Trans feminine patients (Trans women) may have undergone breast augmentation, orchidectomy, facial feminisation surgeries, voice change surgeries, laser hair removals, cosmetic surgery and electrolysis. Trans masculine persons(Trans men) should be asked for history of mastectomy, hysterectomy, oophorectomy, and genital reconstruction. Past and current history of medication use is important as well. Questions regarding hormonal therapy, medical co-morbidities, substance abuse, over the- counter treatment and complementary/alternative medication must be asked. In case of doubt, it is advisable to refer to an endocrinologist.

Psychosocial Health :

Psychological health must be evaluated[6]. Increased rates of suicidal tendencies, anxiety and depression occur among transgender and gender diverse individuals. Quality of well-being can be assessed using validated tools such as WHO-5. Depression can be screened with a simple questionnaire called Whooley's 2-item tool[7]. The Gluco Coper is a validated tool which helps assess coping skills in persons with diabetes[8]. There is a need, however, for an Indian tool to assess the quality of life in transgenders.

Social history should include queries related to sexual orientation, sexual behaviour, partner bonding, partner violence and social acceptance. Instead of loaded questions like 'do you have a husband/wife', the health care provider may enquire whether the patient is in a relationship or is sexually active.

Evaluation and clearance by a mental health provider is an important pre-requisite for initiating cross sex hormone therapy.

Cancer Screening :

Breast cancer screening should be carried out, as per standard of care for cis-gender women, in trans masculine persons. Mammography should be conducted every 2 years for trans feminine persons aged $\geq$50, who have received feminizing hormones for $\geq$5-10years. Cervical screening should be done as per standard of care for all persons with an intact cervix. Many patients may refuse such screening: this should not be taken as a contra-indication for initiation or continuation of testosterone therapy in trans masculine persons[6].

Routine ovarian or endometrial cancer screening is not recommended for low-risk patient. If imaging is required, a trans abdominal or trans rectal ultrasound can be performed. Unexplained vaginal bleeding in a transmasculine person with testosterone-induced amenorrhea must be evaluated in a manner similar to that for cis-gender women[6].

Routine screening for testicular cancer is not indicated for persons with intact testes. It is possible, however, that gender dysphoria may prevent timely self-examination and awareness of testicular lumps. Prostate cancer screening should be done as per standard of care for cis gender men, in trans feminine persons. The intervention threshold of prostate specific antigen (PSA) may be lower in persons on feminizing hormone therapy[6].

Infection Prevention :

Transgender individuals with the history of sexual exposure should also be screened for sexually transmitted diseases, including HIV/AIDS and syphilis as per standard of care. It must be remembered that this community is at high risk of contracting such illnesses. Counselling regarding prevention of sexually transmitted disease is a sensitive (and challenging) subject. Condoms, pre-exposure prophylaxis and post-exposure prophylaxis must be advised as appropriate[9,10].

Hepatitis B and human papilloma virus (HPV) vaccination should be offered[10]. Indian guidelines regarding the universal provision of these vaccines to transgender individuals are lacking.

Metabolic Risk Reduction :

The cardiovascular risk of hormone replacement therapy (HRT) in transgender patients is not clearly known. HRT may elevate serum triglycerides and LDL-C in trans men, though this does not necessarily translate into an increase in adverse cardiovascular event. In trans feminine persons, however, HRT is documented to increase the risk of venous thromboembolism, myocardial infarction and ischemic stroke, in a duration dependent manner. Hence HRT must be individualized based on a patient's goals, the risk/benefit ratio of medications[11].

The desperation and over expectation of transgender patients are real. Some take potentially life-threatening decisions like undergoing illicit surgeries or over the counter medications etc. Our duty is to explain to each patient about the possible risks and adverse effects of the therapy and choose the best option for them.

Persons at high risk of cardiovascular disease must be managed according to standard of care. The indication for aspirin, statins and RAAS blockers are similar in cis-gender and transgender adults. All cardiovascular risk stratification tools are based on binary gender, and will have limited use in screening transgender people.

Osteocrine Health :

Bone health is an area of concern in transgender persons. Individuals who discontinue hormonal regimens after undergoing gonadectomy are particularly at risk. Risk stratification tool such as FRAX (Fracture Risk Assessment Tool) are gender-specific, and may not provide an accurate assessment of a transgender bone health status.

Contraception and Fertility :

Transgender adults of reproductive age group remain fertile, unless they have undergone gonadectomy or hysterectomy. HRT provides a contraceptive effect, but persons who are not on hormonal therapy may need protection against unwanted pregnancy. Condoms and vasectomy in trans feminine persons, and intrauterine devices in trans masculine individuals are other options[9].

Many transgender people will want to sire children. Because feminizing/masculinizing hormone therapy limits fertility, it is desirable to offer the patients options for fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs.

Dermatologic Health :

Skin health issues are frequent in transgenders. Apart from routine illnesses, there are some disorders which are specific to transgender persons, especially those on hormonal therapy. Acne vulgaris and androgenic alopecia can occur in transmasculine persons. Pseudofolliculitis barbae, keloids, melasma (chloasma), lichen sclerosus and silicone reactions are seen in transfeminine individuals. HPV and related skin lesions can be encountered in surgically constructed neovaginas. HIV can present as skin lesions including psoriasis, condylomas, seborrheic dermatitis or dry skin. AIDS can manifest as basal cell, squamous cell or Kaposi's sarcoma[12].

Legal Issues :

Health care professionals should be well versed with current legal requirements before gender reassignment. No intervention, especially surgical or endocrine, should be carried out without informed written consent (or assents, in the case of minors). Multi-disciplinary evaluation, including psychological/psychiatric, surgical and endocrine assessment, is helpful in ensuring safety, for the patient as well as for the health care system[6].

Social Modulation :

Transgender health cannot be optimized unless they are provided with a society and social environment which is friendly and sensitive to their needs. Health care professionals should lead the way in demonstrating the accepting of transgender individuals, through words as well as action. Promotion of transgender health should become an integral part of public health and social medicine.

Limitations :

While India has a significant transgender population, which is visible socioculturally and legally, not much medical and medical anthropological research has been done on them. Transgender medicine is slowly gaining acceptance as part of mainstream endocrinology, but its relevance to primary care has not been highlighted. Keeping these limitations in mind,

this narrative review tries to make health care for transgender persons part of routine medicine.

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Conflict of Interest : None

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- **"Transgender" is an umbrella term that is used to describe individuals with gender diversity.**
- **It includes individuals whose gender identity is different from their birth-designated sex and/or whose gender expression does not fall within stereotypical definitions of masculinity and femininity.**
- **Gender dysphoria or gender incongruence is defined as distress or discomfort that may occur when gender identity and birth-designated sex are not completely congruent.**
- **Transgender individuals should have their gender incongruence diagnosed by medical professionals with appropriate experience.**
- **It is necessary to ascertain that there is persistent gender incongruence and that the person is able to understand the risks and benefits of intervention**
- **Before initiating transgender hormonal or surgical treatment, the clinician should counsel the patient about risks and benefits of the hormonal or surgical therapy, including impact on fertility, as well as realistic expectations about outcomes.**
- **For transgender women (male-to-female [MTF]), we suggest either antiandrogen therapy (spironolactone or cyproterone acetate [CPA]) or gonadotropin-releasing hormone (GnRH) agonist therapy, combined with estrogen therapy (transdermal or oral 17-beta-estradiol)**
- **The use of ethinyl estradiol is avoided in transgender females because of an increased risk of venous thromboembolism (VTE)**
- **Transgender individuals should follow the screening guidelines for all tissues present, independent of expressed gender.**
- **Transgender women receiving hormone therapy should be monitored to avoid supraphysiologic serum estradiol (E2) concentrations (eg, maintain E2 levels <200 pg/mL [734 pmol/L]) and to verify that serum testosterone levels reach the normal physiologic female range.**
- **Serum potassium should be checked in those taking spironolactone, and monitor serum prolactin and triglycerides because of exogenous estrogen administration.**
- **Gender confirmation (or affirmation) surgeries can be considered after living one year in the desired gender role and after one year of continuous hormone therapy.**
- **For transgender men (female-to-male [FTM]),either testosterone esters (administered intramuscularly or subcutaneously) or testosterone gels are used depending upon patient preference.**
- **Transgender men receiving testosterone therapy be monitored for erythrocytosis and dyslipidemia, two potential adverse effects of androgen therapy.**

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Systemic Review Article

A Brief Outline of COVID 19 Specific Therapy in Hospitalised Patients In India

Syamasis Bandyopadhyay[1], Tanushree Mondal[2], Susobhan Mondal[3]

COVID 19 pandemic has a significant impact on global public health and economies. Scientists and researchers all over the world are endeavouring in search of specific drug against COVID19 virus. For a novel emerging virus, specific antiviral drug takes time before its approval for clinical use as RCTs are expensive and time consuming. In Indian perspective, many drugs which are currently under clinical trial are unavailable. Reviewing available published and unpublished papers, we intend to throw light on the drugs that can be used in the interim in India till further evidence come. Pending sufficient evidence remdesivir, favipirvair,tocilizumab,lopinavir-ritonavir with or without ribavirin; hydroxychloroquine or convalescent plasma can be considered.

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Key words **: COVID 19, COVID 19 treatment, Lopinavir-ritonavir, Hydroxychloroquine in COVID-19, Hydroxychloroquine prophylaxis, Remdesivir, Favipiravir, tocilizumab, Dexamethasone, Convalescent plasma in Covid 19.**

The COVID 19 pandemic has a significant impact on global public health and economies.

Coronaviridae family is an important pathogen that primarily affects respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which were epidemic in nature. In December 2019, in Wuhan, Hubei province, China a cluster of patients were admitted with influenza like illness or severe acute respiratory syndrome. The common source of the infection was found to be a seafood and wild wholesale market in Wuhan. The pathogenic virus for the illness was first identified as Novel Corona virus (2019-nCov) and later it was renamed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co V2) after the genetic sequencing.

The first case of the COVID-19 in India was reported on 30 January 2020, in a patient returned from China. As of 5 July, 2020, the Ministry of Health and Family Welfare have confirmed a total of 244,814 active cases, 409,082 recoveries (including 1 migration) and 19268 deaths in the country. At the time of writing, the World Health Organisation (WHO) reported 11,125,245 confirmed cases including 528,204 confirmed deaths globally and 217 countries, areas or territories reporting cases.

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Editor's Comment :

- **Physicians should remain flexible in adopting protocols for treatment based on evolving evidence.**
- **Properly designed RCTs on covid19 specific therapy will possibly change treatment strategy based on strong evidence.**

Such unparallel worldwide effect of the SARS- CoV-2 pandemic has prompted scientific community to explore all possible solutions as there is no evidence based specific antiviral drugs or vaccine against COVID-19 infection till date. Out of many possibilities available, an antiviral drug remains the most crucial option. An effective, safe, and available treatment strategy for the disease is the need of the hour.

Several treatments are being evaluated worldwide. Multiple drugs with in-vitro antiviral activity against SARS-CoV-2 and/or immunomodulatory effects that may have clinical benefit are being tested and their use in COVID 19 patients remain investigational. Some of the drugs are in the verge of getting approval from the respective drug licensing authority but are currently unavailable in India. In Indian scenario the COVID19 specific therapy is likely governed by availability of treatment, established evidence and affordability.

For a novel emerging virus, specific antiviral drug

takes time before its approval for clinical use as RCTs are expensive and time consuming. The drugs which act on similar pathogen and have broad spectrum activity is considered in the interim.

Triple combination therapy (Lopinavir-ritonavir+ ribavirin+interferon beta 1b) :

In a recent multicentre randomised open-label phase 2 trial in patients with COVID-19, triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were found to be more effective and safe to lopinavir–ritonavir alone when introduced early in the disease i.e. within 7 days of the onset of symptoms. The triple combination alleviates symptoms more readily and discontinue viral shedding and facilitates hospital discharge[1]. Interferon beta-1b should not be continued after 7 days of onset of symptoms because of its pro-inflammatory effect. The common side effects were nausea (35%) and diarrhoea (40%), increased alanine aminotransferase (13%) and fever (37%) with no serious adverse event noted. The level of IL 6 was also lower in the triple drug regimen group than the control group.

In India Interferon beta-1b is scarcely available but combination of ritonavir + lopinavir and ribavirin available. So initiation of treatment with double agent lopinavir -ritonavir and ribavirin as early as possible preferably within 7 days of onset of symptoms in the moderate to severe hospitalised patients if there is no contraindication to their use can be considered.

WHO is currently collecting data for SOLIDARITY. "Solidarity" is an international clinical trial to help find an effective treatment for COVID-19, launched by the World Health Organization and partners.Following treatment options were selected in the solidarity trial: Remdesivir; Lopinavir/Ritonavir; Lopinavir/Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxy-chloroquine.WHO removed lopinvar-ritonavir combination from SOLIDARITY trial on the basis of interim reports of the trial and review of the evidence of all trials on the first week of July,2020 as lopinavir-ritonavir combination did not show reduction in mortality in hospitalized patients when compared with standard of care[2].

The RECOVERY trial in UK concluded which they published on 29 June, 2020 that there was no clinical benefit of lopinavir-ritonavir combination in terms of 28 day mortality, risk of progression to mechanical ventilation or duration of hospital stay[3].

Hydroxychloroquine/Chloroquine:

The potential mechanism of action of CQ/HCQ against SARS-CoV-2 is essentially postulation. The virus enter cells by binding to a cell surface receptor called angiotensin-converting enzyme 2 (ACE2). SARS Co-V2 also upregulates the ACE2 expression. Chloroquine may reduce glycosylation of ACE2, and thus prevent SARS Co-V2 from effectively binding to host cells and entering the cell[4]. Savarino et al. hypothesise that CQ might blunt the production of pro-inflammatory cytokines, thereby inhibiting the pathway that subsequently leads to acute respiratory distress syndrome (ARDS). Some viruses enter host cells through endocytosis and is transported within the host cell via endosome, within which the virus can replicate. When the endosome fuses with the acidic intracellular lysosome, this leads to rupture of the endosome with the release of the viral contents. Chloroquine increase the pH of the endosome and interferes with this process[5].

Hydroxychloroquine (HCQ) appears to have more potent antiviral activity than chloroquine(CQ), although clinical evidence of CQ/HCQ on COVID-19 is variable and does not show any clear benefit. In one unpublished randomized trial adding hydroxy-chloroquine to standard treatment in of patients with mild COVID-19 pneumonia without hypoxia resulted in improvement of symptoms and chest imaging findings[6]. In another unpublished randomized trial there was no improvement in terms of discontinuing viral shedding or symptoms on adding hydroxychloroquine to standard treatment by 28 days in hospitalized patients with mild to moderate COVID-19[7].

Published clinical data on CQ/HCQ are limited and have methodologic problems. In an open-label study, use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with higher rate of viral clearance at day 6 compared with no specific treatment (70 versus 12.5 percent)[8]. On other hand in a randomized trial in Shanghai, there was no such difference observed in viral clearance at day 7 with hydroxychloroquine 400mg per day for 5 days compared to standard treatment.Other antiviral agents including interferon were used in both arms, which could have confounding effects[9].

Additionally higher risk of intubation or death (hazard ratio [HR] 2.37) was found in an observational study with use of hydroxychloroquine in patients with COVID19[10] but this had bias as patients who received hydroxychloroquine were older and have comorbidities with introduction of the drug was at later stage. In a multivariate analysis comparing those patients with a propensity score-matched subset who did not receive hydroxychloroquine, there was no association between hydroxychloroquine use and intubation or death

(adjusted HR 1.04).

The RECOVERY trial in UK found no benefit in 28-day mortality or hospital stay or other outcomes in patients receiving hydroxychloroquine in the treatment arm[11].

WHO removed hydroxychloroquine arm from the SOLIDARITY trial on the first week of July, 2020 on the basis of interim reports of the trial as hydroxy chloroquine did not show any clear evidence of reduction in mortality when compared with standard of care. However, the decision is applied only for SOLIDARITY trial[12].

Hydroxychloroquine as prophylaxis :

The basic criteria of a drug that can be used as a pre-exposure prophylaxis is following: 1) Safety profile. 2) Ease of use. 3) Suitable pharmacokinetics and pharmacodynamics. 4) Efficacy and 5) Cost-effectiveness

As HCQ satisfies the above criteria and the selectivity index(Selectivity index is ratio between cytotoxicity and antiviral activity) of HCQ is relatively low, HCQ can be considered in line of prophylaxis till more evidence come where a steady concentration of HCQ can be achieved over a period of time to prevent virus from binding to host cells and also to resist the virus at post entry level. It requires more clinical trials and careful planning to use HCQ as an effective treatment option.

Hydroxychloroquine with azithromycin :

One French study used azithromycin in combination with hydroxychloroquine which was associated with more rapid viral clearance than hydroxychloroquine alone[13], but that study had methodologic concern. Another study failed to show rapid RNA clearance with the combination[14]. We should be aware that both the agents cause prolongation of QTc and hence careful monitoring is needed when this combination is used.

Hydroxychloroquine with Zinc supplementation :

As CQ/HCQ specifically target extracellular zinc to intracellular lysosomes where it interferes with coronavirus replication and zinc deficiency is common in elderly patients and in patients with comorbidities like diabetes, chronic obstructive airway disease, it can be hypothesized that CQ/HCQ with zinc supplementation may be more effective in antiviral activity than CQ/HCQ alone. More studies are required to establish the hypothesis.

Remdesivir :

Remdesivir potently blocks SARS-CoV-2 infection with a high selectivity index. Holshue et al. reported that intravenous remdesivir yielded promising results in the COVID-19 patients[15].

In a study published in Lancet by Yeming Wang *et al*[16], found remdesivir was not associated with clinical benefits of statistical significance. In that trial the patients were with standard care with use of lopinavir-ritonavir, corticosteroid and interferon.

In a summary of subjects receiving remdesivir as compassionate use in USA, nearly 70% of patients had improvement in oxygen requirements and early intubation was seen in on mechanical ventilation. This report had no control group; hence interpretation is difficult. It is early to conclude direct antiviral effect of remdesivir on enhanced viral clearance from respiratory tract, but it suggests promising therapeutic effect[17].

The United States launched Adaptive Covid 19 Treatment Trial (ACTT) to evaluate experimental treatment for COVID-19 under supervision of National Institute of Health. An independent data and safety monitoring board on interim analysis on remdesivira nnounced that remdesivir was better than placebo from the perspective of primary end point ie, time to recovery. Recovery was defined as being well enough for discharge from hospital or returning to normal activity level. In patients treated with remdesivir median time to recovery was 11 days compared to 15 days in placebo group. The study group had 31% faster recovery placebo ($p<0.001$). Moreover preliminary results showed improved mortality rate 8.0% for the drug for the study group versus 11.6% for placebo ($p=0.059$)[18].

The Food and Drug Administration (FDA) approved emergency use of remdesivir in treatment of severe COVID-19 which is defined as SpO2<94% in ambient air, requiring supplemental oxygen, mechanical ventilation or ECMO. The Indian Council of Medical Research (ICMR) also has fast-tracked the roll out of global ''Solidarity'' trial by the World Health Organisation (WHO) which includes remdesivir.

Favipiravir :

Favipiravir (FPV) is a guanine analogue which is approved for influenza since 2014 has shown in vitro inhibition of SARS-CoV-2[19].

In an open label clinical trial by QingxianCai *et al*[20]. FPV arm with interferon alpha showed significantly higher improvement radiologically and also faster viral clearance when compared with liponavir-ritonavir plus interferon alpha. There were fewer adverse events in

the FPV arm compared to control arm.

The possible adverse effect of favipiravir are hyperuricaemia, teratogenicity and QTc prolongation but generally has favourable safety profile. Further, evidence is needed to consider favipiravir as a recommended option against Covid 19.

One Indian Pharmaceutical company has initiated Phase-3 clinical trials in India on antiviral tablet Favipiravir, for which it received approval from India's drug regulator DCGI in late April.

Convalescent plasma :

In an uncontrolled casese ries of 5 SARS C- V2 patients with rapidly progressive acute respiratory distress syndrome (ARDS) with severe pneumonia and high viral load despite antiviral treatment, administration of convalescent plasma containing neutralizing antibody resulted in improvement in the patients' clinical status in terms of defervescence, improved PaO2/FiO2, SOFA score and negative viral load. However, the trial sample size was limited with no controls and the subjects were on other antivirals as well[21].

In another study, 6 COVID-19 subjects with respiratory failure received convalescent plasma at late stage (at a median of 21.5 days after first detection of viral shedding) and all tested negative for SARS-CoV-2 RNA by 3 days after infusionbut 5 patients died eventually thus questioning its effectivity at later stage. It seems thatconvalescent plasma therapy should be initiated as early as possible in hospitalised patients as it does not reduce mortality in critically ill patients but can decrease viral load[22].

The adverse effect of plasma therapy are infection with other pathogen via transfusion, as with any other blood product and hazard of blood product transfusion like transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI). A theoretical concern about the convalescent plasma is potential worsening of immune-mediated tissue damage via antibody-dependent enhancement as well as blunting of endogenous immunity to the virus. Blood product transmission of the SARS-CoV-2 virus has not been documented yet and is very unlikely for a respiratory virus.

Finding appropriate donor with suitable neutralizing antibody is the main challenge in this therapy and also quantitative serologic assays to identify donors with high titre neutralizing antibodies are not yet widely available.

ICMR has given permission for a multicentric phase-2 trial using convalescent plasma on COVID-19 patients with moderate illness, which is currently recruiting.

Tocilizumab :

In severe COVID 19 cytokine storm occurs which is characterized by increased level of interleukin-6 (IL6) and inflammatory markers such as D-dimer and ferritin that lead to ARDS (acute respiratory distress syndrome) and multiorgan failure and causes mortality. Based on this observation blocking of inflammatory pathway to treat COVID19 has been postulated. Tocilizumab in an IL-6 receptor inhibitor which is approved by FDA for the treatment of cytokine release syndrome and other disorders like giant cell arteritis and rheumatoid arthritis.

In an open label study in China 21 patients of COVID 19 with severe oxygen impairment, high CRP and lymphopenia on receiving tocilizumab resulted in improved oxygenation, normalisation of CRP and normalisation of lymphopenia in significant percentage of patients. Absorption of opacity of lung lesion in the CT scan occurred in 90.5% of patients[23].

In a single arm pilot prospective open label study 63 patients with severe COVID 19 disease received tocilizumab and there were improvement in ferritin, CRP, D-dimer and oxygenation(PaO2/FiO2). There was no significant adverse effect[24].

Dexamethasone :

The RECOVERY trial in UK a total of 2104 patients were randomised to receive dexamethasone with a dosing regimen 6mg once daily PO/IV for 10 days and compared with 432 patients on usual care. Dexamethasone reduced death rate in one third of ventilated patients, in one fifth of patients requiring oxygen support and showed no beneficial effect in patients who did not require oxygen support. Based on the results one death can be prevented when treated around eight ventilated patients and around twenty-five patients requiring oxygen support[25]. To determine the subset of patients who will mostly benefit from dexamethasone additional details are needed.

Itolizumab :

Itolizumab is a 'first in class' humanized IgG1 monoclonal antibody which selectively targets CD6, a pan T cell marker involved in co stimulation, adhesion and maturation of T cells. It inhibits the pro-inflammatory cytokine and can be useful option to treat cytokine storm due to COVID 19. Trials in Delhi and Mumbai have been started. Apart from India, the trial on Itolizumab is also ongoing in Cuba.

Conclusion:

With the studies and trials published so far and other preliminary reports several therapeutic options can be used as per physician's discretion though till date, there are no specific evidence based medicines for COVID-19 available. Multiple treatments are under investigation, and will be tested through observational study and RCTs. Pending sufficient evidence, the following drugs and combination of drugs can be considered for treatment for COVID 19 in hospitalised patients in India:

Limitations of the study :

The following are the limitations of this review:

(1) Specific therapy on COVID 19 is evolving continuously. Best choices will keep on changing depending on accrued evidence.

Drugs	Dose and duration	Adverse effect	Remarks
Lopinavir-ritonavir+ Ribavirin	Lopinavir-ritonavir : PO lopinavir 400 mg and ritonavir 100 mg every 12 h for 14 days Ribavirin : PO 400 mg every 12 h for 14 days Interferon beta 1b: 1 mL (8 million international units [IU]) on alternate days subcutaneously for 3 doses twice	Nausea, diarrhoea, increased alanine aminotransferase and fever	The three-drug regimen preferably should be used within 7 days of onset of symptoms. If started within 7 -14 then interferon beta 1 b should be omitted. **This drug has been omitted from SOLIDARITY and RECOVERY trial because lack of beneficial effect.**
Hydroxychl-oroquine	PO 200 mg twice per day for 5 d	Nausea, diarrhoea, prolonged Qtc, bradycardia	Zinc can be combined with HCQ. **HCQ has been omitted from SOLIDARITY and RECOVERY trial because lack of beneficial effect.**
Remdesivir	IV 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin	Remdesivir is currently available in India. Costly drug. To consider using in severe COVID19
Favipiravir + Interferon alpha	Favipiravir PO Day 1: 1600/ mg twice daily; Days 2–14: 600/ mg twice daily) plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily)	hyperuricaemia, teratogenicity and QTc prolongation	Favipiravir is currently available in India
Convalescent plasma	2 consecutive transfusions of 200 to 250mL of ABO-compatible convalescent plasma (400mL of convalescent plasma in total) on the same day it was obtained from the donor.	Transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI)	To continue other antiviral medications as well
Tocilizumab	IV: 8 mg/kg (maximum: 800mg/dose) as a single dose : may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve (Genentech 2020)	Showed no significant adverse effect related to tocilizumab in the published trials in COVID 19 patients. Hypersensitivity, hepatic injury, cytopenia, GI perforation, increased risk of infection are the concerns related to adverse effects. Relapse of tuberculosis or activation of latent tuberculosis and malignancy are the concerns who receive tocilizumab for other indications.	Costly drug. Currently under SOLIDARITY and RECOVERY trial
Dexame-thasone	IV/PO: 6mg once daily for 10 days	Adverse report was not reported (including secondary infections)	Not indicated in patients who do not require respiratory support

(2) As the published studies on COVID 19 are mostly observational and the RCTs are confounded with limitations, lack of systematic review or metaanalysis makes review articles open for further discussions.

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Voice of the Expert

COVID 19 Vaccine — Hope & Hype

Dr Ravi Wankhedkar is a name which needs no introduction. A past national president of the IMA (2018), he is a successful practising surgeon of Maharashtra. He is a polymath in all sense of the term, with active involvement in multiple socio-cultural activities. He is particularly involved in medical services among the poor of his home town. The **JIMA** editorial board discussed various aspects of the current pandemic with Dr Wankhedkar recently. The interview was conducted by **Prof Jyotirmoy Pal** and final copy editing was done by **Dr Rudrajit Paul**. The excerpts of that interview are presented here, exclusively for the readers of **JIMA**.

Dr Wankhedkar, welcome to JIMA. We are honoured to be allowed this privilege of talking with you. First, can you tell us your general thoughts on the current scenario ?

Ans : - With no control of the pandemic in sight, desperation and fatigue has set it.

All of us feel that a vaccine will be the key to the EXIT strategy to return to normal.

This is mostly true. But there are many uncertainties which we all need to understand about vaccines as 'The ' ultimate answer to the current crisis. There are complexities of developing a vaccine at ultra-short notice.An effective vaccine that is too complex to make in bulk, or is difficult to formulate, is highly unstable withoutrefrigeration or freezing, is challenging to administer or that requires too many doses over a prolonged period may represent a Pyrrhic victory for science, but not the answer to the problems faced by the societies that science serves.

Q1 - We know it is very difficult to make predictions. But, still our readers would like to know when will the vaccine be available ?

Scientists are surging forward with possible COVID-19 vaccines,but they've still got a long way to go.In the history of medicine, rarely has a vaccine been developed in less than five years.Enormous amounts of public money and resources poured into vaccine research and development have resulted in more than 150 COVID-19 vaccine candidates, ten of which are now in clinical trials.

The most advanced candidate is AZD1222, first developed by researchers at the University of Oxford. Developing a successful vaccine is hit or miss under any circumstances. And SARS-Cov-2 is a fickle and baffling new virus.If everything goes smoothly you might know as early as start of next year you have a vaccine that's likely to be effective. Normally safe vaccines take years to develop but thx to modern technology & Augmented Intelligence scientists hope they can now be developed within a year.

Indeed, the story of vaccine development is largely the story of failure.

Most research efforts end where they begin -in the lab.It can be very difficult to find the weak spot in a virus and how to get the immune system to launch a counter-attack. Many viruses also mutate, making them harder to disable. That's proven to be particularly true of HIV/AIDS.Some research efforts do produce experimental vaccines, and they often work well in animals. But then they fail in humans.Scientists have a phrase for it: " Mice lie, monkeys exaggerate "

Editorial note : Vaccine development takes a lot of time. In spite of repeated attempts, vaccines for HIV, dengue or malaria are still elusive. So, only vaccine development should not be the crux of all efforts. We should try other avenues like anti-virals too. during the 1897 plague epidemic of India, the British government touted anti-plague vaccine as a cure-all. But the efficacy of that vaccine was doubtful.

Q2 - Will it be effective ?

Vaccines induce immunity. What will be the type, effectiveness and duration of this immunity is

important. Ideally, vaccines would prevent infection entirely, inducing what's known as "sterilizing immunity."But early work on some of the vaccine candidates suggests it will give " protective immunity " - they may not stop infection in the upper respiratory tract but will prevent it from infecting lower resp tract, thus preventing severe complications & mortality. Whether a single dose of vaccine will give life long immunity or like Flu vaccine it will have to be taken yearly is to be seen. It's likely that vaccination won't be a one-time affair. As the virus changes and immunity wanes, people will need to be immunized again. There's no telling how often that will have to happen, though studies of other coronaviruses suggest that immunity could last for a few years.

Q3 - Will the vaccine be safe ?

Vaccines have to be very safe and effective. If a vaccine isn't manufactured correctly, it can hurt or kill people.Unlike with drugs, you're administering them to healthy people !We can administer untested n unproven drugs as treatment as life saving measure, but same cannot be true for giving vaccines. History is replete with complications of vaccines which may be counterproductive. In the rush to be the first in discovering vaccine , Safety can't be overlooked. "The ' biggest challenge' will come once an Effective & Safe vaccine is discovered "Meeting the overwhelming demand for a successful coronavirus vaccine will require a historic amount of coordination by scientists, drug-makers and the government.The nations supply chains need to be ready for such an effort.

Q4 - How much doses will be required ?

It depends on the timeline. To achieve Herd immunity we need approx 60-70 % of population to be infected naturally or by vaccines. Since 20% or more may have been infected naturally by that time, we'd need to get perhaps 40% utilization to achieve herd immunity.Still that translates to Billions of doses manufactured, packaged, stored, delivered, & administered. We need to ramp up those abilities while we're figuring out the science.

Q5 - Who are the people who will get it first ?

Equitable access to the vaccine and deciding priorities will be the million dollar question. The WHO is drawing up plans to determine who will receive a COVID-19 vaccine first if one is approved, with frontline workers, vulnerable groups, and those working or living in high-transmission settings first in line.It is imperative that more governments and pharmaceutical companies need to commit to WHO allocation guidelines and cooperate globally to distribute vaccines fairly to those at greatest risk. A pandemic vaccine needs strong global governance behind it.

There are many multi country international coalitions working towards it likeGAVI(the vaccine alliance),Operation Warp Speed (USA),Global Vaccine Summit + Gates Foundation- GAVI Covax AMC (Advance Market Commitment) and others.

While global cooperation is welcome, Unfortunately many rich countries have already entered into deals with various vaccine developers for availing vaccine when developed.

Editorial note : It is indeed an unfortunate lesson of human history that the people who need a resource the most have usually the least chance of accessing it. That is why organizations like WHO or UNICEF have to ensure equitable distribution.

Q6 –what may be the probable Cost of this new vaccine ?

Huge financial stakes are involved. The first companies to develop and manufacture safe, effective vaccines can expect to cash in big time.It's unclear what the vaccine will cost consumers. But investors say the market will entail hundreds of millions — and possibly billions — of people who will want the vaccine.

Q7 –what will be the Logistics required for this new vaccine? Will India be able to cope with the demands ?

Vaccinating billions of people involves a logistical nightmare and may require years. Manufacturing, Packing, Transporting,Training health care workers, Acceptance by society,Costsetc presents problems.

Polio took 60 years to eradicate after vaccine was developed !This issues will be best tackled by the melding of minds irrespective of wherever the bodies are geographically located.

Q8 - Will Vaccine Alone control Covid 19 ?

Developing a vaccine will be a major break through for control of Covid but vaccine alone may not be sufficient. Effective, Safe, Affordable drugs +

Change in human behaviour+ Robust Public Health systems are must along with vaccines for prevention and treatment of Covid.

Although a vaccine was crucial for ending smallpox, it was not enough on its own.

"After all, the vaccine was first developed by Edward Jenner in 1796. It took another 184 years for smallpox to be eradicated"

Q9 - What if Vaccine is not discovered ?

It will not be the end of road. We don't have vaccines for many many recurring diseases including viral infections like HIV. Effective drugs and public health measures can still bring Covid 19 to manageable levels.

Q10 –what are your thoughts on the Anti Vaccination Movement ?

Vaccine hesitancy or anti-vax, is a reluctance or refusal to be vaccinated or to have one's children vaccinated against contagious diseases despite the availability of vaccination services. Based on irrational unscientific Misunderstandings & Misinformation plus Religious beliefs is fuelling this movement.

Many believe that vaccines will cause the disease itself or have complications like autism or will be ineffective or that this entire pandemic is a hoax and is a conspiracy of giant pharma companies.

It was identified by the WHO as one of the top ten global health threats of 2019.Inspite of all these doubts and obstacles ,Vaccine still remains our best hope to return to normalcy.

With advancement in science and technology we hope to have a vaccine by year end or early next year. Global Solidarity,Cooperation and humanitarian approach riding over politics & economics is the need of hour.Till then Physical distancing, Hand hygiene, Masks and the strategy of Test-Trace- Isolate- Treat remains our only hope.

Editorial note: In India, many practitioners of alternative medicine sometimes decry the use of vaccines. These unscrupulous people often promote "natural" immunity boosters and the public are often misled by them. The editors of JIMA would like to stress repeatedly that there is no alternative to vaccines. Vaccines have helped mankind overcome the scourge of deadly diseases like measles and polio. If these alternative medicine charlatans get their foothold in the sphere of public discourse, and the public start believing them, irreversible damage to public health will occur.

Q11 – What is your impression regarding recent hype on Indian vaccine development ?

Vaccine development in India -

Much media hype was created by the ill timed, unnecessary and wrongly worded ICMR letter. Due to opposition by the medical fraternity and scientists luckily government did some damage control and gave lame explanations about it.

Hopefully Vaccine will be developed in India latest by early next year. Two companies are working on it and have entered phase 1 clinical trials. Depending on results of phase 1, they will go in phase 2 and then in phase 3.

Safety of vaccines is of utmost importance and no one should bypass the established time tested procedures.

Editorial note :

Few uncertanities

1. COVID-19 Viral Immunology not clearly understandable.

2. Wheather antibody that is produced after infection or vaccination is protective or not and if protective - how long will persist not clear.

3. Trial of each phase has uncertainty.

4. Safety of any trial has utmost concern.

Dr Wankhedkar, thank you for the valuable insight into immunology and vaccine development of Covid-19.

Original Article

Study of plasma fibrinogen levels with Hypertension, Dyslipidemia, BMI, and Glycemic status in type 2 Diabetes Mellitus

Anil Samaria[1], Meenakshi Samaria[2], Mahveer Prasad Sharma[3], Yogesh Meena[4], K K Parikh[5], Girish Mathur[5], G D Ramchandani[6]

Introduction : A prospective study of correlation of plasma fibrinogen with Blood Pressure, BMI, and lipid profile and glycemic status in type 2 Diabetes Mellitus (DM).

Method : The study included 100 cases of type 2 diabetes mellitus that attended the outpatient and admitted as in patient at Jawaharlal Nehru Medical College and Associated Group of Hospitals, Ajmer. A detailed history and physical examination was done ie, measurement of blood pressure and anthropometric measurements as height, weight and body mass index. Laboratory Investigation like plasma fibrinogen, serum lipid profile, blood sugar and HbA1c was done.

Result : Detailed Statistical analysis was done and the data that emerged from the study was represented in the form of statistical table and geographical plates.

Conclusion : The study shows increase in plasma fibrinogen level with age and more in hypertensive than normotensive. There was also positive correlation with BMI and HbA1c lead to increase in plasma fibrinogen. There is also positive correlation with serum cholesterol and triglyceride level and negative correlation with serum HDL.

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Key words **: Diabetes, Hypertension, Dyslipidimia, Fibrinogen.**

During past decade the potential role of haemostatic factors particularly fibrinogen in various disorders and their complication has gained considerable interest. The plasma fibrinogen predicts cardiovascular events in both general population and diabetics and non diabetics with clinical vascular disease.

Elevation of fibrinogen level and impaired fibrinolysis are more common in diabetic than non diabetics. Increase plasma fibrinogen concentration with those of other acute phase reactants in the emerging view of sub clinical inflammation as a characteristic of and possibly a risk factor for type 2 diabetes mellitus.

Fibrinogen is an acute phase reactant synthesized in the liver and comprise of 2 to 3% of plasma protein. Fibrinogen is associated with various pathophysiological processes. It is involved in coagulation, blood rheology, platelet aggregation, and endothelial dysfunction. Fibrinogen is a component of atherosclerotic lesion at every stage of evolution even at the earliest.

A relationship between fibrinogen and cardiovascular disease was first described in 1950s when plasma fibrinogen was slightly elevated in patient with IHD.

In the present study an attempt is made to correlate the level of fibrinogen with blood pressure, BMI, smoking, history of hypertension and lipid profile and glycemic status of the patient

Aims and Objective

1. To know the fibrinogen levels in patients of type 2 diabetes mellitus
2. To correlate plasma fibrinogen levels in patients of type 2 diabetes mellitus with blood pressure body mass index, lipid profile and glycemic status.

Editor's Comment :

- Hypertensive, Diabetic, Obese & dyslipidemic Patients have increased plasma fibrinogen levels it can be used as a marker of metabolic syndrome.

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Material and Method

A prospective study of Correlation of Plasma Fibrinogen with Blood Pressure, BMI, Lipid Profile and Glycemic Status in type 2 diabetes mellitus in JLN Hospital, Ajmer over a period of 15 month from June 2013 to August 2014. The study included outpatient and inpatient at Jawaharlal Nehru Medical College and associated Hospital. Patients informed consent taken. Detail history and physical examination done along with anthropometric measurement. Laboratory data included blood sugar HbA_1C lipid profile, and plasma fibrinogen level. Other additional investigation was done wherever they needed. Plasma fibrinogen level was done by thrombin clotting method by fibroquant kit.

Z test, CHI square test and Pearson correlation coefficient have been used to find the significant of study parameter statics software PRIMER an SPSS version 20 were used for the analysis of data and Microsoft word and excel have been used to generate graph and tables.

Result

1. In the present study 63 were male patient and 37 were female patients. In these 25 were of 40-49 age group, 39 were age group of 50-59, 22 were of 60-69, 12 were of 70-79, and 2 patient were of >80.
2. In the present study there was age related increase in plasma fibrinogen level among type 2 diabetes mellitus patient. The patient in the age group of 40-49 years showed (6.17± 1.27g/l) plasma fibrinogen level. The patient in the age group of >80 years had (7.10± 0.14g/l).
3. In this study female patient shows comparatively higher level than male patient. Female patient shows (6.47±1.72 versus 5.80±1.57) from male.
4. Mean level of plasma fibrinogen with family history of hypertension and diabetes compared to those without family history (7.45±1.10 versus 5.12±1.98g/l). Out of 100 patient 26 patient had family history of diabetes or hypertension or both.
5. Among 63 male patient 33 were smoker and 30 were non smoker the smoker had (6.90±1.01g/l) fibrinogen level compared to (4.32±1.15g/l) level in non smokers.
6. From total 100 patient 62 had hypertension and hypertensive patient had (6.26±1.67g/l) level compared to patient without hypertension (5.75±1.40g/l).
7. In this study BMI of patient ranges from 17.58 to 38.26kg/m^2 and fibrinogen level ranges from (5.65±0.65 to 7.00±1.15g/l). BMI more than 30kg/m^2 had higher fibrinogen level (7.00±1.15) compared to those with less body mass index.
8. From total 100 patient maximum number patient had serum level of cholesterol of 150-199 and mean plasma fibrinogen level in range of (5.76±1.43)g/l and the patient had serum cholesterol level of 250-299 with mean plasma fibrinogen level of (7.41±1.82)g/l.
9. The patient who had serum triglyceride level between 100-149 had plasma fibrinogen level about 3.19±0.15g/l and those with serum triglyceride level more than 400 mg/dl had (9.80±0.85g/l) plasma fibrinogen level.
10. In this present study patient with HDL level 30-34mg/dl with mean plasma fibrinogen level (6.63±1.72g/l) and patient had HDL level 45-49 had mean plasma fibrinogen level of (4.39±1.10g/l).
11. In this present study total 37 patient had LDL cholesterol level 50-99 had mean plasma fibrinogen level of (5.73±1.47g/l) with 54 patients having mean plasma fibrinogen level of (6.10±1.55g/l).
12. In comparison of plasma fibrinogen level with glycolsylated haemoglobin level 13 patient having HbA1c level 6.0-6.9 have mean plasma fibrinogen level of (3.55±0.34g/l), 29 patient had HbA1c level 7.0-7.9 had plasma fibrinogen level of (4.96±0.52g/l), 48 patient having HbA1c level 8.0-8.9 had mean plasma fibrinogen (7.08±0.59g/l) 8 patient having HbA1c level 9.0-9.9 had mean plasma fibrinogen level of (8.43±0.16g/l), and 2 patient having HbA1c level of >10 had mean plasma fibrinogen level of (8.43±0.16g/l).

Discussion

Fibrinogen which was earlier found to be raised in inflammatory condition but now it has emerged as one of the cardio vascular risk factor. So it has gained much more importance today. Patient with high fibrinogen level are more prone to develop myocardial infarction, stroke and peripheral vascular disease.

1. In this present study age group of the patient range from 40-85 years and maximum no. patient were seen in age group of 50-59 sex distribution show male predominance. The result shows age related increase level of plasma fibrinogen from (6.17±1.27 to 7.10±0.14g/l) this is possibly due to age related decrease in fibrinogen degradation.
2. Female are having more level of plasma fibrinogen level compared to men (6.47±1.72 versus 5.80±1.57g/l). May be due to the structural difference in fibrinogen which resist the lysis of fibrinogen lead to increase level and addition of two allele possibly lysine which causes functional difference in fibrinogen level which causes reduce incidence of IHD, STROKE and PVD.

3. There is higher mean plasma fibrinogen level in patient with family history of hypertension and diabetes compared to those without family history (7.45±1.10 versus 5.12±1.98g/l) these incidence of heritability suggest genetic component may be a contributor.
4. In this study patient of diabetes with duration of diabetes ranging from the less than one year to twenty five year patient with longer duration having decrease level of fibrinogen possibly due to use of insulin lead decrease in fibrinogen survival.
5. There is higher level of fibrinogen in smoker than non-smoker. Smoker had (6.90±1.01 versus 4.32±1.15g/l) possibly smoking lead chronic stimulation of monocyte which secrete the IL-6 which increase the synthesis of fibrinogen level.
6. In our study, higher plasma fibrinogen levels were noted in type-2 diabetic patients with hypertension compared to normotensives. Out of 100 patients, 62 patients had hypertension. The difference in plasma fibrinogen levels among hypertensive and normotensive patients was statistically insignificant (6.26±1.67 versus 5.75±1.40; p>0.05).
7. Glycosylated haemoglobin showed a linear correlation with plasma fibrinogen level in this study. Mean plasma fibrinogen value increased as HbA1C value increased.
8. The body mass index (BMI) was correlated in each patient and was correlated with plasma fibrinogen levels and found that there was positive correlation between BMI and plasma fibrinogen level. All the patients with BMI more than 30 Kg/m2, had significantly higher plasma fibrinogen levels, compared to others.
9. In the present study, serum lipids were measured in each patients such as serum cholesterol, triglyceride, HDL and LDL and their correlation with plasma fibrinogen level was ascertained. The positive correlation was found between cholesterol level, LDL level and triglyceride levels and negative correlation between HDL level and plasma fibrinogen level. Possible explanation for increase level of fibrinogen level in this metabolic syndrome condition is that these conditions are associated with low grade inflammatory response which releases the cytokines like interleukin 6, tumor necrosis factor-alpha which lead to increase fibrinogen level which can be reversed by increase in physical activity.

Conclusion

The study shows increase in plasma fibrinogen level with age and more in hypertensive than normotensive. There was also positive correlation with BMI and HbA1c. Increase in BMI and HbA1c lead to increase in plasma fibrinogen. There is also positive correlation with serum cholesterol and triglyceride level and negative correlation with serum HDL.

Funding : None

Conflict of Interest : None

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Original Artcle

A Study of the Effect of Metformin *Versus* Myo-Inositol in the Management of PCOS — A Randomised Controlled Trial

Subesha Basu Roy[1], Shilpa Basu Roy[2]

Of the common hormonal disorders in females of childbearing age-group, polycystic ovary syndrome (PCOS) is the most important. It is associated with various morbidities like type-II diabetes mellitus, obesity, insulin-resistance, cardiovascular dysfunctions and is characterised by reproductive and psychological manifestations, resulting in an enormous impact on health. The objective of our study was to compare the efficacy of metformin and myo-inositol on certain parameters such as BMI reduction, LH/ FSH ratio (suggesting insulin resistance) and HOMA-IR Index in PCOS patients. In our study, both metformin and myo-inositol significantly reduced the BMI. Metformin also significantly reduced the insulin resistance and improved insulin-sensitivity. It also significantly improved menstrual pattern in the women with PCOS. These changes were not observed when treated with myo-inositol. The sample size calculation was done with n Master 2.0 Christian Medical College, Vellore.

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Key words **: Polycystic Ovary Syndrome, PCOS, Metformin, Myo-inositol.**

Editor's Comment :

- **Polycystic ovary syndrome (PCOS) is a common cause of menstrual irregularity and infertility**
- **Diagnosis of the disease is commonly done with the help of Rotterdam criteria**
- **Metformin and Myo-inositol are the main drugs used in therapy**
- **Weight loss is also an important component of management**
- **Confounding factors like hypothyroidism needs to be ruled out before diagnosing PCOS**

An approximate 10-20 percent of ladies in the reproductive age-group are affected by polycystic ovary syndrome (PCOS). PCOS is the commonest cause of anovulatory infertility and is also called hyperandrogenic anovulation. Insulin-sensitizing agents are amongst the recommended treatment options for the hyperinsulinemia induced ovarian dysfunction, resulting in improved response to gonadotropinsin PCOS.This in turn, helps in restoration of normal menstrual cycle and ovulation, and thus increases the chance of spontaneous pregnancy. In 2003, the Rotterdam Consensus of the European Society of Human Reproduction and Embryology (ESHRE) & the American Society for Reproductive Medicine (ASRM) reached a general agreement on the diagnostic criteria for this syndrome. Metformin and myo-inositol are the main treatment options available in the management of PCOS (Fig 1).

Materials and Methods

The present study was an open-label randomised controlled trial which was carried out at the department of obstetrics and gynaecology, IPGME&R & SSKM Hospital, Kolkata. Our study was conducted during a period of 2 years. It comprised of 306 PCOS patients (as per the Rotterdam Criteria), of whom 153 belonged to the group treated with Metformin and the remaining 153 belonged to the group treated with Myo-inositol. Patients who presented to the Gynaecology OPD in IPGME&R with suggestive symptoms of oligo-anovulation (amenorrhoea, oligomenorrhoea, polymenorrhea, menorrhagia), hyperandrogenemia (example hirsutism, acne, infertility) and USG features suggestive of PCOS were included. Patients less than 18 years of age and the post-menopausal women were excluded in the study. Other criteria for exclusion from the study were patients with uncorrected hypothyroid status, or pregnant patients, or those who were diagnosed with CAH (congenital adrenal hyperplasia), prolactin secreting adenomaor diabetes mellitus. Patients who were already on treatment for PCOS were also excluded from our study.

The parameters such as height (in metre), weight (in kilogram) were recorded and BMI (Basal Metabolic

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Index) was calculated. A detailed history including patients' menstrual history (such as amenorrhea, oligomenorrhea and irregular cycles), infertility, features of hyperandrogenemia (such hirsutism, acanthosis nigricans) were noted. Investigations such as-assessment of LH (luteinizing hormone), FSH (follicle-stimulating hormone), serum prolactin and serum insulin were done.

The two groups were subjected to the following treatment schedule (all medicines were supplied free of cost from the hospital pharmacy) -

Metformin group : Metformin (500mg) thrice daily for 3 months.

Myo-inositol group : Myo-inositol (2 gram) twice daily for 3 months.

After three months of treatment, the following parameters were analysed and compared statistically between the two groups: BMI reduction, LH/ FSH ratio (suggesting insulin resistance) and HOMA-IR Index(Homeostatic Model Assessment of Insulin Resistance). HOMA-IR Index is used for quantifying IR (Insulin Resistance) and beta cell function. It is calculated by: HOMA-IR = (glucose X Insulin) / 405 (glucose in mg/dl).

Appropriate standard statistical tools were applied for analysis of the observed data.

Results

The total number of PCOS patients in our study was 306. Of them 153 patients were advised metformin (500mg) thrice daily for 3 months (Metformin group) and the remaining 153 patients were advised myo-inositol (2 gram) twice daily for 3 months (Myo-inositol group).

In theMetformin group,the mean BMI was 28.12 before treatment. It reduced to 26.05 after 3 months of treatment. This was a statistically significant finding. The mean HOMA-IR index was 4.65 before treatment. It was reduced to 2.23 after treatment, i.e., statistically significant. The mean LH/ FSH ratio, which denoted insulin-resistance, was 2.36 before commencing treatment. It decreased to 1.6 post-treatment. This observation was also statistically significant.

In the Myo-inositol group,the mean BMI was 24.45 before treatment and it was decreased to 23.05 after completion of treatment. This observation was statistically significant. The mean HOMA-IR index was 2.02 before treatment. It was reduced to 2.00 after treatment. This finding was not statistically significant. The mean LH/FSH ratio was 2.02 before starting treatment. It diminished to 2.00after three months of treatment, ie, which was not statistically significant.

Discussion

In our study, it was observed that the mean BMI, LH/ FSH ratio and HOMA-IR index grossly improved in the PCOS patients who were treated with metformin (Metformin group). These findings were statistically significant. In the patients who were treated with myo-inositol (Myo-inositol group), although the mean BMI reduced significantly, the mean LS/ FSH and mean HOMA-IR index failed to show any change. Thus, it was apparent in our study, that myo-inositol was ineffective in reducing insulin-resistance in the PCOS patients.

Numerous studies have been conducted in the past to analyse the efficacy of metformin in the management of PCOS. Velazquez *et al*[1] were amongst the first to show a 35% reduction in the area under insulin curve and a 31% decrease in insulinarea to glucose area ratio, thus indicating the improved insulin-sensitivity in PCOS patients treated with metformin. Lord *et al*[2] in their meta-analysis, revealed that metformin was effective in decreasing fasting insulin levels and hence

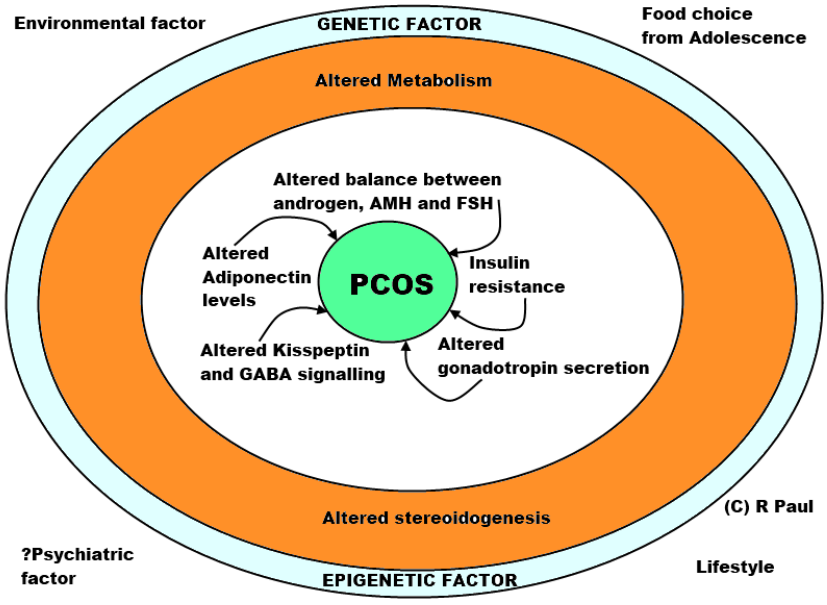

Fig 1 — The Pathophysiology of PCOS : schematic representation

was an effective treatment option for anovulation in PCOS.

Although in our study, myo-inositol did not show any improvement in the insulin-sensitivity in the PCOS patients, but some studies have demonstrated the contrary. For instance,Galazis *et al*[3], showed that treatment with myo-inositol improved insulin-resistance in PCOS patients.In another study by Constantino *et al*[4], 42 PCOS patients were treated with myo-inositol. It was found that the fasting serum insulin and glucose levels remained unchanged. About 69.5%had their ovulation restored.Teede *et al*[5] recommended that inositol (in any form) should be considered an experimental remedy for treating PCOS. In a study by Gerli *et al*[6], the BMI significantly improved in the patients treated with myo-inositol, but the waist-to-hip ratio remained unchanged.

A randomized, placebo-controlled, double-blinded study by Tang *et al*[7] on obese PCOS patients treated with metformin alone or combined with lifestyle modifications, assessed the effects on anthropometry, metabolism, and menstruation. They concluded that metformin alone did not improve weight loss or menstrual regularity in the concerned patients. Significant improvement in menstrual health was achieved by weight loss alone through lifestyle changes.

Conclusion

From our study, it is evident that metformin is an excellent choice in the treatment of PCOS. It effectively reduced BMI and insulin-resistance in the PCOS patients. It also concluded that myo-inositol was effective in significantly reducing the mean BMI. However, in the myo-inositol group, there was no effect on HOMA-IR index or mean LH/ FSH ratio thus suggesting its ineffectiveness in improving insulin-sensitivity in the patients with PCOS. So myo-inositol can be a good treatment option for reducing BMI or it may be used in combination with an insulin-sensitising agent like metformin in the treatment of PCOS, but not used alone.

Funding : None

Conflict of Interest : None

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Original Artcle

Etiological study of seizure disorders among patients attending the epilepsy clinic of an urban center in Eastern India

Sankhapani Mishra[1], Atanu Roy Choudhuri[2], Madhab Kumar Mandal[3], Udas Chandra Ghosh[4], Sudipta Mondal[5]

Background : The etiology of seizures range from perinatal hypoxia and developmental disorder in neonates, febrile seizures in children, CNS infections, trauma, head injury and brain tumors in adolescence, and cerebrovascular accidents and Alzheimer's disease in the elderly. Understanding the etiology of seizure is useful in clinical practice, to fine tune therapeutic interventions.

Materials and Methods : We studied 85 new cases attending the Epilepsy Clinic of Bangur Institute of Neurology, Kolkata and Murshidabad Medical College, Berhampore for one year, and attempted to establish the etiology of seizures in this population.

Results : Out of the 85 cases enrolled 39 (46%) had generalized seizures and 46 (54%) suffered from localization related epilepsy (focal or partial seizures). Analysis of our data revealed that idiopathic seizures were the commonest (85%), followed by congenital (10%), vascular (1%) and degenerative (1%), among cases with generalized seizures. However, among the patients presenting with partial seizures, idiopathic, congenital and degenerative were equally common (20% each), followed by traumatic (13%), neoplastic (10%) and infective (9%).

Conclusions : Idiopathic causes are more important in the domain of generalized seizures while secondary causes like idiopathic, congenital and degenerative etiologies tend to be more common in partial seizures.

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Key words **: Epilepsy , Seizure disorder, Etiology of seizure disorder, Seizure semiology.**

In ancient Greece as now people spoke of "having seized" and of having had an "attack"[1]. Epilepsy is a group of neurologic conditions, the common and fundamental characteristic of which is recurrent, usually unprovoked epileptic seizures. Epileptic seizure represents the clinical manifestation that result from excessive synchronous, abnormal firing patterns of neurons that are located predominantly in the cerebral cortex. Such abnormal paroxysmal activity is usually intermittent and self limited[1,2,3]. In 1981, the International League Against Epilepsy (ILAE) published a modified version of International Classification of Epileptic seizures in 1981 and revised expanded version in 2017 that still provides the fundamental of seizure classification till date[4,5] (Tables 1&2).

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Editor's Comment :

- **The etiology of seizures remains unknown in most clinical care settings.**
- **This study documents that, among patients presenting with seizures, the commonest cause seems to be idiopathic, followed by congenital, degenerative, traumatic and neoplastic in decreasing order of frequencies.**
- **Focusing on generalized seizures, the idiopathic form dominates further, followed by degenerative as a relatively remote cause.**
- **In contrast, when partial seizures are considered in isolation, idiopathic, congenital and degenerative causes seem equitably distributed as common entities, followed by traumatic, neoplastic and infective causes, in successive decreasing sequence.**

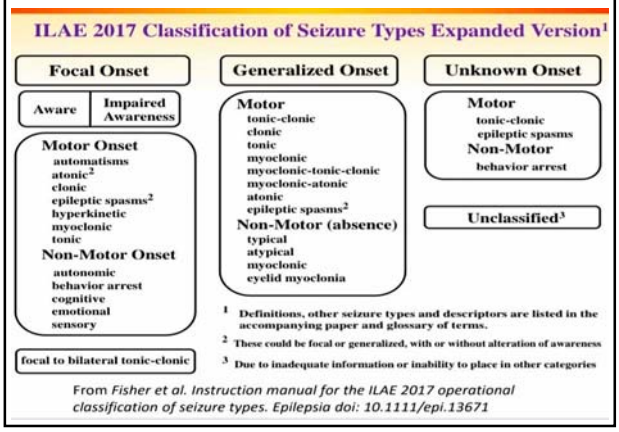
Materials and Method

This was a hospital based observational study conducted at the Epilepsy Clinic of Bangur Institute of Neurology, Kolkata, and the Departments of Physiology and Medicine, Murshidabad Medical College, Berhampore, over a period of one year. 85 consecutive new patients attending the clinic with undiagnosed seizure disorders were selected and seizure type established through detailed history and clinical examination. Patient suffering from syncope,

Table 1 — *ILAE classification of seizures, 1981*

Partial seizures	• Simple partial seizure • Complex partial seizure • Partial seizure with secondary generalization
Primarily generalized seizure	• Generalized tonic clonic seizure • Tonic seizure • Atonic seizure • Myoclonic seizure • Absence seizure
Unclassified seizure	• Neonatal seizure • Infantile spasm

Table 2 — *ILAE classification of seizures, 2017*



From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

conversion disorder, heart block, movement disorders and metabolic disorders likely to precipitate seizures were excluded from this study. Appropriate blood tests along with EEG, brain CT Scans (plain and contrast) and brain MRI were performed to establish the cause of the seizures.

Results and analysis

The mean age in our study population was 38.7 ± 8.2 years, with the mean age among cases with generalized and partial seizures being 49.2 ±7.8 and 29.6 ± 5.5 years respectively.

Out of the 85 cases enrolled 39 (46%) had generalized seizures and 46 (54%) suffered from localization related epilepsy (focal or partial seizures) (Fig 1). Among those with generalized seizures, 33 had idiopathic seizures while only 9 had idiopathic seizures among those with partial seizures, giving a total of 42 cases (49%) of idiopathic seizures in the study. The other common etiologies of seizures in the study population were congenital (15%), degenerative (12%), traumatic (7%) and neoplastic (6%) (Table 3, Fig 2).

Analysis of our data revealed that idiopathic seizures were the commonest (85%), followed by congenital (10%), vascular (1%) and degenerative (1%), among cases with generalized seizures. However, among the patients presenting with partial seizures,

Table 3 — *Etiology of seizures in study population (n = 85)*

Etiology	Incidence	Etiology	Incidence
Idiopathic	42 (49%)	Traumatic	6 (7%)
Congenital	13 (15%)	Neoplastic	5 (6%)
Degenerative	10 (12%)	Infective	4 (5%)
Vascular	3 (4%)	Others	2 (2%)

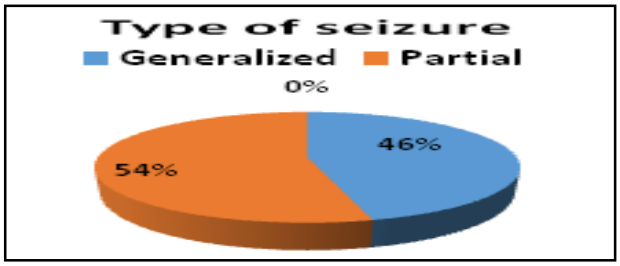


Fig 1 — Distribution of generalized and partial seizures in the study

idiopathic, congenital and degenerative were equally common (20% each), followed by traumatic (13%), neoplastic (10%) and infective (9%) (Table 4). The etiology of seizures was much diverse in the partial seizure subgroup in contrast to the overwhelming majority of idiopathic seizures among those with generalized seizure presentation.

Discussion

Despite the plethora of knowledge on this subject, a substantial percentage of patients will remain classified as suffering from idiopathic seizures[6]. Looking into the genetic basis of seizures, different studies have made it clear that seizure are caused mostly by polygenic defects[7,8,9]. All factors that can affect the brain ie, head trauma, neoplasms, degenerative diseases, infections, metabolic diseases, ischemia and hemorrhages etc can predispose a person to epilepsy[10]. It is also known that certain brain areas eg, temporal and frontal lobes are more susceptible to produce epileptic seizure activity than the others.

We performed a detailed neurological workup before investigations in our effort to establish the cause of seizures. The neurological examination assesses focal

Table 4 — *Seizure etiology among patients with generalized and partial seizures*

	Generalized seizures (n = 39)	Partial seizures (n = 46)
Idiopathic	33 (85%)	9 (20%)
Congenital	4 (10%)	9 (20%)
Vascular	1 (2.5%)	2 (4%)
Neoplastic	0	5 (10%)
Degenerative	1 (2.5%)	9 (20%)
Infective	0	4 (9%)
Traumatic	0	6 (13%)
Others	0	2 (4%)

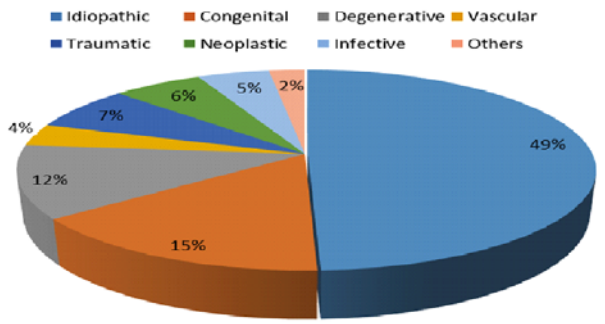


Fig 2 — Etiology of seizures in study population (n = 85)

signs that might implicate or localize cerebral pathology. Increased tone on one side of the body could indicate pathology in the contralateral hemisphere, such as a cortical dysplasia. The general physical examination is also important to determine whether the patient has an underlying condition. Abnormal skin markings could indicate a neuro-cutaneous disorder in which epilepsy is common, such as tuberous sclerosis or neurofibromatosis.

In a study from Rochester, Minnesota, the incidence of partial seizure was 57%, generalized seizure 40% and 3% was unclassifiable[11]. Our data is similar to this experience with 46% having generalized and 54% partial seizures at presentation. The preponderance of idiopathic seizures in the generalized seizure subgroup is in keeping with data from across the world. Even in the developed nations, population studies reveal no identifiable cause of seizures in 55% to 89%. However, the proportion of cases with an antecedent identifiable cause of seizure is relatively consistent, ranging from 23 – 39%.

Among the patients presenting with partial seizures in our study, idiopathic, congenital and degenerative were equally common (20% each), followed by traumatic (13%), neoplastic (10%) and infective (9%). This is in keeping with international trends where more identifiable causes can be established during the management of partial seizures, as opposed to the management of generalized seizure disorders. It is also important to note that despite the study being conducted in a government teaching hospital of India, infections contribute relatively less to the etiological spectrum of seizure disorders. It is well known that infections like Tuberculoma, HSV encephalitis or brain abscess may all present with partial seizures. These, along with other causes of seizures, are important to identify as potentially treatable with appropriate medical or surgical options.

Age remains an important consideration in the management of seizures. In children epilepsy associated with neurological deficits from birth was found to be the most important single etiological relationship, whereas cerebro-vascular disease is the most commonly identified cause among adults. In the renowned Rochester, Minnesota study conducted between 1935 and 1984, 65.5% of seizures were idiopathic/cryptogenic, 10.9% were of vascular origin, 8% congenital, 5.5% traumatic, 4.1% neoplastic, 3.5% degenerative and 2.5% infective[10]. An identifiable lacunae in our study was the selection of cohort from a tertiary level referral clinic which does not reflect the population at large.

Conclusions

We conclude that partial seizures are commoner than generalized seizures, and tend to occur in younger age groups. Idiopathic causes are more important in the domain of generalized seizures while secondary causes like idiopathic, congenital and degenerative etiologies tend to be more common in partial seizures.

Limitations of study :

(1) Only patients attending tertiary care centre were taken.

(2) Everyone could not afford MRI (at that time MRI was not free).

(3) Some of the patients did not had the patience for MRI.

(4) CT SCAN could not be done in patients less than 1 year of age due to radiation hazard.

Funding : None

Conflict of Interest : None

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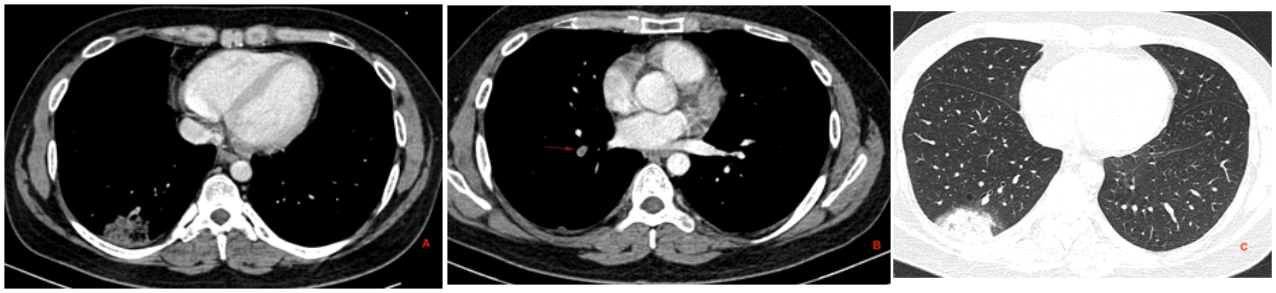
Image of Medicine

Quiz 1

Bhoomi Angirish[1], Bhavin Jankharia[2]



CT scan axial images of a 40 year old man with acute onset of breathlessness.

Questions :

(1) What is the diagnosis?

(2) What is the name of the X-ray sign for pathology shown in image a & c?

(3) What is the clue to diagnosis on CT scan images (image a & c)?

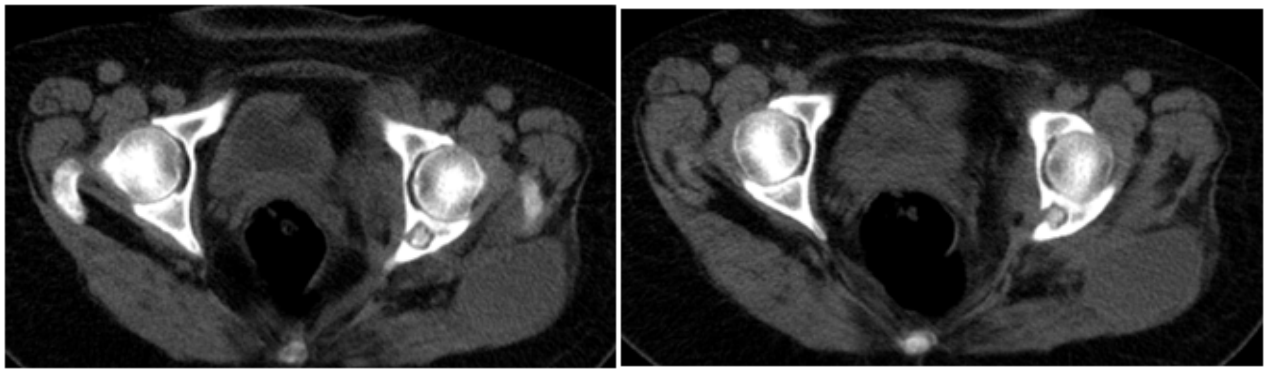
Answers:

(1) Pulmonary thromboembolism with pulmonary infarct.

(2) Hampton hump – It referes to pleural based wedge shaped / rounded opacity due to pulmonary infarction.

(3) Bubbly consolidation or central lucencies within the infarcted lung parenchyma, best appreciated on mediastinal window images is the clue to diagnosis of pulmonary infarct. It is hypothesised to represent coexistence of aerated non-infarcted lung with infarcted lung in the same pulmonary lobule due to dual blood supply by pulmonary vascular and bronchial vascular system.

Quiz 2



CT scan axial images of a 33 year old lady presenting with pain and swelling in left gluteal region.

Questions:

1) What is the diagnosis?

2) Name the sign shown in the image.

3) What are the differential diagnosis of this lesion?

Answers:

1) Osteolytic lesion with sequestrum in posterior left acetabulum along with collection in gluteal region. Biopsy was performed from the lesion and gluteal collection was aspirated - the results of which confirmed tubercular osteomyelitis.

2) Bony sequestrum – It refers to calcification within lucent lesion, often completely separated from surrounding bone. Pathologically sequestrum refers to a piece of devitalised bone with necrosis and resorption that has been separated from its surrounding bone.

3) Bony sequestrum is often present in osteomyelitis and skeletal tuberculosis. The other conditions which mimic sequestrum are eosinophilic granuloma, lymphoma, metastasis and malignant fibrous histiocytoma. Some primary bone tumors like osteoid osteoma can also mimic bony sequestrum.

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 2 :

ECG

Clue :"ABnormal Left"

This is the ECG of 60 y old female with chest pain;

Diagnosis from limb leads only.

Questions:

1. What are ECG findings?
2. Why is this clue?
3. What is Practical implication?

Answers :

ECG FINDINGS :

The limb leads show in this ECG shows left ward axis with no significant changes in QRS, ST or T waves. The important features in this ECG is P wave is tallest in L I rather than in L II. In normal ECG,P wave is tallest in LII. Rarely, if there is left axis deviation of P wave, P wave may be taller in LI. In addition to this, the P is inverted with terminal positivity with negative QRS in LIII. So, this combination of ECG findings is suggestive of left arm, left lower limb lead reversal.

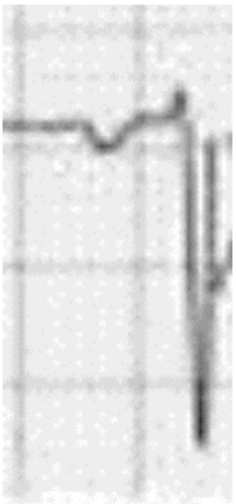


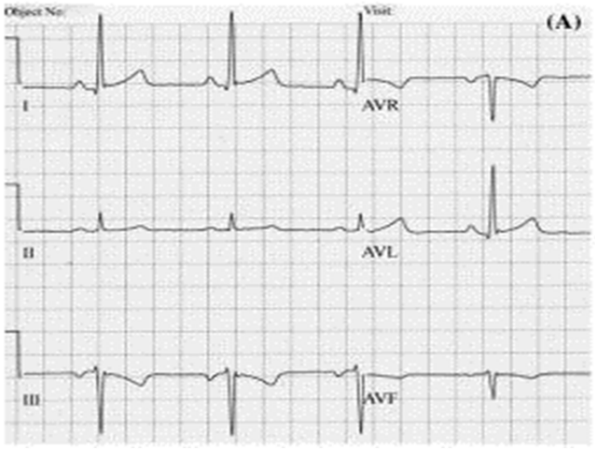
Fig.68A. Inverted P with terminal positivity and negative QRS in LIII.

As the left arm lead is in the lower limb and the left lower limb lead in the left upper limb, L I becomes L II and L II becomes L I. Hence, the P wave is directed to L I in this ECG, which is the real L II in normally recorded ECG. Here L III is reversed (LA in lower limb) and that's QRS is negative in LIII. The peculiarity of inverted P wave is the terminal positivity of P wave.(68A)

THE CLUE :

The 3 important signs of this ECG indicating LA, LL leads reversal are:

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



1. Tall P wave in L I ,
2. Negative QRS in L III
3. Inverted P with terminal positivity in LIII.

So these 3 ECG signs are named as "Abdollah sign". Because of this, "ABnormal left" clue is given to indicate Abdollah sign (AB) and abnormal lead connection on left side.

PRACTICAL IMPLICATION :

These subtle ECG findings are often missed and may be wrongly diagnosed as IWMI sometimes. So whenever the P wave is taller in LI than LII, look at LIII for inverted P with terminal positivity and negative QRS. This means Left Arm, Lower Limb lead reversal. The correctly recorded ECG is shown in ECG 62B.

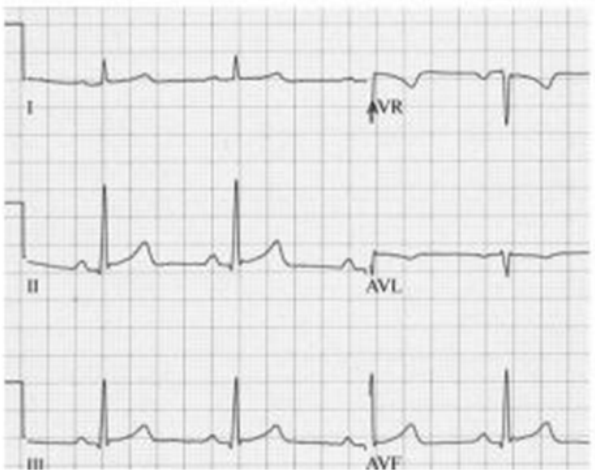


Fig.68B: Correctly recorded ECG of the same patient.

Case Report

Adenocystic carcinoma of palate masquerading benign cystic palatal lesion : A rare case report

Rohit Bhardwaj[1], Ankur Gupta[2], Kirti Khandelwal[3], Sabarirajan Ponnusamy[4], Chirayata Basu[4], Karthika Nathan[4]

Adenocystic carcinoma (ACC) is a rare epithelial malignancy of salivary gland origin, accounting for <1% of all head & neck malignancies. Palate is a preferred site. It shows female predominance, preference in 5th and 6th decade of life, slow growth rate, perineural invasion, distant metastasis and potential for local recurrence. Surgery with radiotherapy is the treatment modality of choice. We present a case of 34 years old female, who was diagnosed to have an infected cystic lesion on FNAC. HPE of resected specimen confirmed it as ACC. Patient received combined treatment (Surgery + Radiotherapy), and now free of disease even after 2 years of follow up. [*J Indian Med Assoc* 2020; **118(7):** 48-50]

Key words **: Adenocystic carcinoma (ACC), epithelial malignancy, minor salivary glands, perinural invasion, local recurrence.**

Adenocystic carcinoma (ACC) is a rare epithelial malignancy of salivary gland origin. It accounts for less than 1 % of all head and neck malignancies & almost 10 % of salivary gland tumours belong to this variety[1]. It mainly affects minor salivary glands however sites of respiratory tract like larynx & lungs have also been reported to be involved by ACC owing to the presence of submucosal or seromucinous glands[2]. The preferred location of this tumour is palate, especially area of junction between soft and hard palate[3]. Demographically females are affected more by ACC, in 5th or 6th decade of life[4]. Tumour usually follows a slow growth pattern with indolent disease course which makes it look more like a benign rather a malignant lesion & can be held responsible for its delayed presentation. ACC has gathered various names based on its histological studies which includes basiloma, cylindroma, adenoepithelioma and adenoid basilod carcinoma[5]. Histopathological classification holds prognostic values for ACC[6]. Based on histology this tumour has three varients i.e. cribriform, tubular and solid. Cribriform or "swiss cheese" variant is most common and also has the best prognosis. A single tumour can show more than one histological pattern. A peculiar feature of this tumour is the neurotropic tendency for metastasis[7]. Gasserian ganglion has been reported to be the intracranial site involved by ACC[8]. Lymphatic and haematogenous spread occurs rarely, however cases of distant metastasis to bone, lungs and soft tissues by haematogenous route exists[9]. Tumour can be dealt with either by single modality (Surgery/ Radiotherapy/ chemotherapy) or as combined therapy[10]. Wide local excision with adequate margins and post op radiotherapy is the preferred modality of treatment for this tumour[11]. We present a case of 34 years old lady who was misdiagnosed based on disease course and FNAC findings and had to undergo repeat surgical excision of the lesion.

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Editor's Comment :

- **ACCs are very much capable of masquerading a benign lesion because of its slow growth rate, indolent course, asymptomatic presentation (most of the times) and cellular pleomorphism leading to inaccurate histo-pathological diagnosis on FNAC or small punch biopsy.**
- **A low threshold for combining radiotherapy along with surgery for treatment should be practiced since the tumour has recurrence potential. I hope this delivers the desired information. I hope for the positive response from your esteemed journal with respect to this article.**

Case Report

34 years old lady presented to our outpatient department with complain of a slowly progressing swelling on left side of palate for past 8 months. She experienced no pain, difficulty in chewing / swallowing or loosening of teeth and any other swelling in head and neck region. She never had smoking, alcoholism and tobacco chewing habits. On detailed clinical evaluation she was found to have a soft to firm swelling involving left side of soft palate (Fig 1). Swelling measured approximately 3cm X 2cm & had smooth surface. This non mobile swelling did not have ulcerations on surface. Patient had carious teeth. No other swelling or neck lymph nodes were palpable. Palatal movements were also bilaterally symmetrical. Nasal endoscopy also failed to report anything relevant.

Fine needle aspiration cytology was done from the lesion. FNAC reported the lesion as benign appearing squamous cells and polymorphs in a mucoid background

suggestive of a benign infected cystic lesion. A contrast enhanced computed tomography scan also reported this as a 'well-defined hypodense lesion' approx. 31 cm x 23cm, showing minimal post contrast enhancement of 10-15 HU, suggestive of benign nature of lesion (Fig 2).

Based on clinical and radiological evaluation, patient was planned for complete surgical excision of this benign palatal lesion. The lesion was excised meticulously without damaging macroscopically uninvolved palatal musculature and surgical site repaired primarily to avoid any fistula formation (Fig 3). Histopathological examination of this specimen reported it as an adenocystic carcinoma with positive tumour margins.

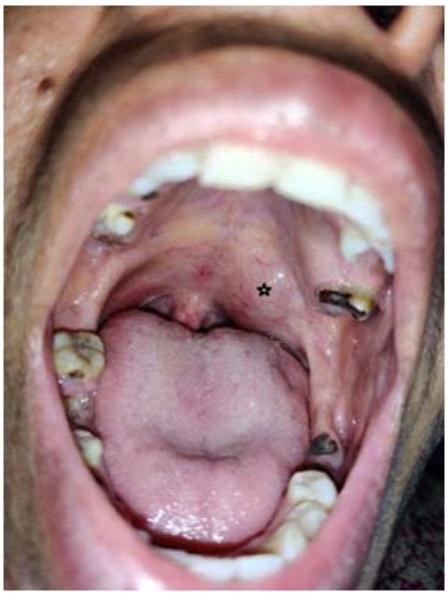

Fig 1 — Showing preoperative palatal swelling, marked by star

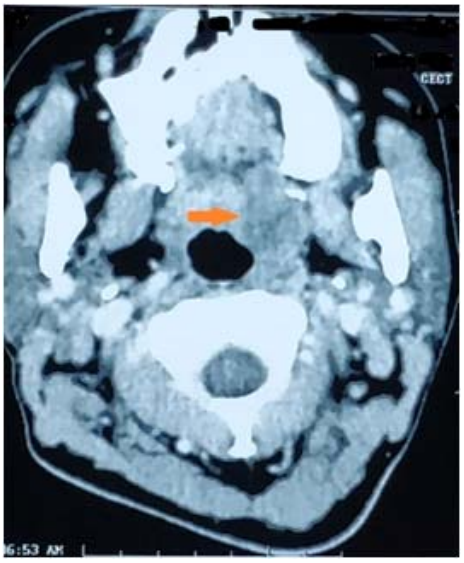

Fig 2 — Showing CT appearance of the lesion marked by solid arrow

After discussing the nature of disease and possibility of palatal defect following revision surgery with patient, she agreed for complete surgical excision of the tumour. We excised the palatal tissue taking adequate margins all around the previous surgical site (Fig 4). Considering the large size of the palatal defect intraoperatively, no attempts of primary repair were made. HPE revealed uninvolved margins all around the lesion; even the nearest positive margin had a disease free distance of >10mm.

Later patient also received radiotherapy to further sterilize the surgical site in an attempt to minimize the chances of recurrence. Excision of carious teeth was advised by dental surgeons prior to radiotherapy but patient denied for this. She developed trismus following surgery and radiotherapy which was dealt by active mouth opening exercises. Prosthesis was made to overcome the difficulties caused by palatal defect (Fig 5). She has been under our follow up for past 3 years and is free of recurrence.

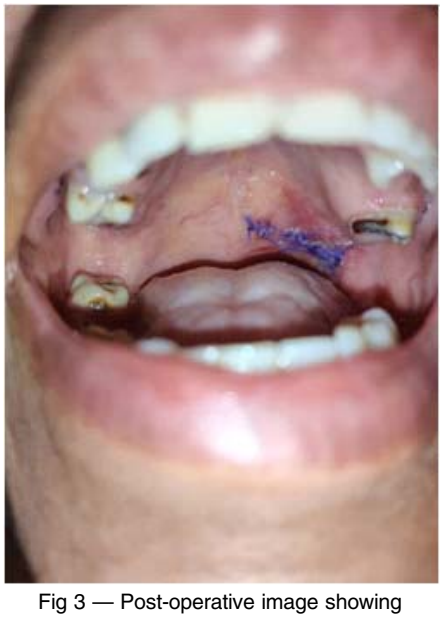

Fig 3 — Post-operative image showing repaired surgical site

Discussion

ACCs usually arise in intercalated ducts of the mucous secreting glands from a cell type which can differentiate in either epithelial or in myoepithelial cells. Owing to the cellular origin, these tumours are mainly confined to minor and major salivary glands and mucous secreting glands of respiratory tract[12]. Since these tumours have a slow indolent course, they are seldom diagnosed early, more so when the palatal is involved. As the palatal lesions are mostly asymptomatic and appear as submucosal, smooth surfaced swellings without having any overlying ulceration, delayed diagnosis is not so uncommon. Besides this, tumour histology also contributes in this diagnostic confusion. The microscopic architectural patterns of this tumour can show wide variations; individually these variations might fail to suggest the malignant nature of the lesion. FNACs and small incisional biopsies obtained away from the true representing area, report inaccuracies in diagnosis owing to this pleomorphism (a confusing feature of these tumours). We hold these factors attributable to the delayed presentation and the misdiagnosis in our case. MRI has a role in describing the soft tissue extension and perineural invasion

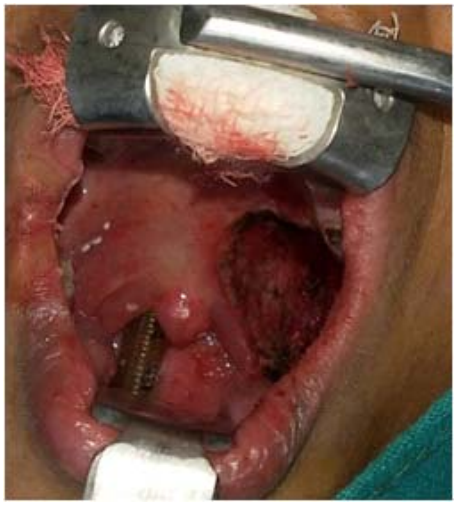

Fig 4 — Intraoperative photograph showing completely resected tumour margins

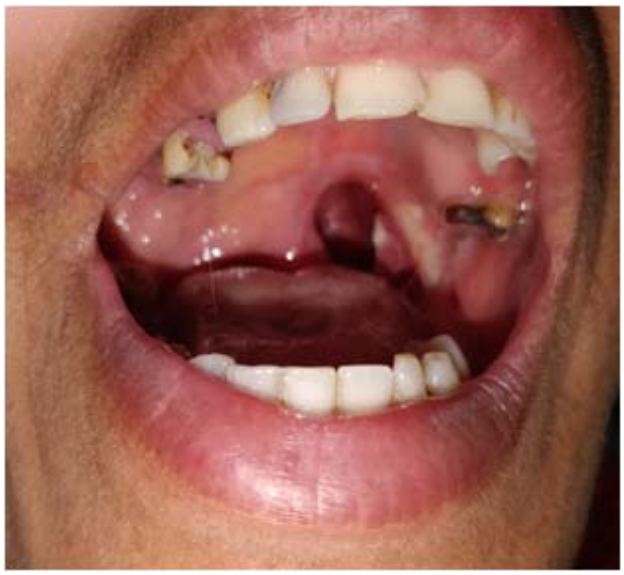

Fig 5 — Photograph showing palatal fistula

while CT helps in showing the bony involvement, besides being important in surgical planning and follow up. ACCs also appear as benign on CT unless the lesion ulcerate or cause bony destruction, this also happened with our case where radiology also suggested a possibility of benign nature of the lesion. Detailed histopathological evaluation of the excised specimen reported the lesion as ACC. While searching for the optimal treatment modality for the tumour, we found diverse opinions in literature. Possible treatment options are surgery, radiotherapy and chemotherapy as a single modality or combination of these. Surgery (wide local excision along with adequate safety margins) was favored by few authors[13,14]. Others proposed combining the two, as surgery or radiotherapy alone is not sufficient enough to prevent disease recurrence and distant metastasis[15]. Owing to its slow growth rate, the response of ACCs towards chemotherapy was not very convincing[16]. After analyzing the various prognostic factors like histopathological grade, cervical lymphatic metastasis, surgical margins & microscopic perineural invasion with respect to our case, we discussed it with radiotherapy team in multidisciplinary team meeting and decided to re-excise the tumour margins and subject the patient for radiotherapy to sterilize the tumour bed. After receiving this combined duel modality treatment, patient is free of any recurrence even after 3 years.

Conclusion

ACCs are very much capable of masquerading a benign lesion because of its slow growth rate, indolent course, asymptomatic presentation (most of the times) and cellular pleomorphism leading to inaccurate histopathological diagnosis on FNAC or small punch biopsy. This calls for a high index of suspicion for diagnosing these lesions. We also recommend a low threshold for combined or duel modality treatment (surgery along with radiotherapy), since the tumour has recurrence potential.

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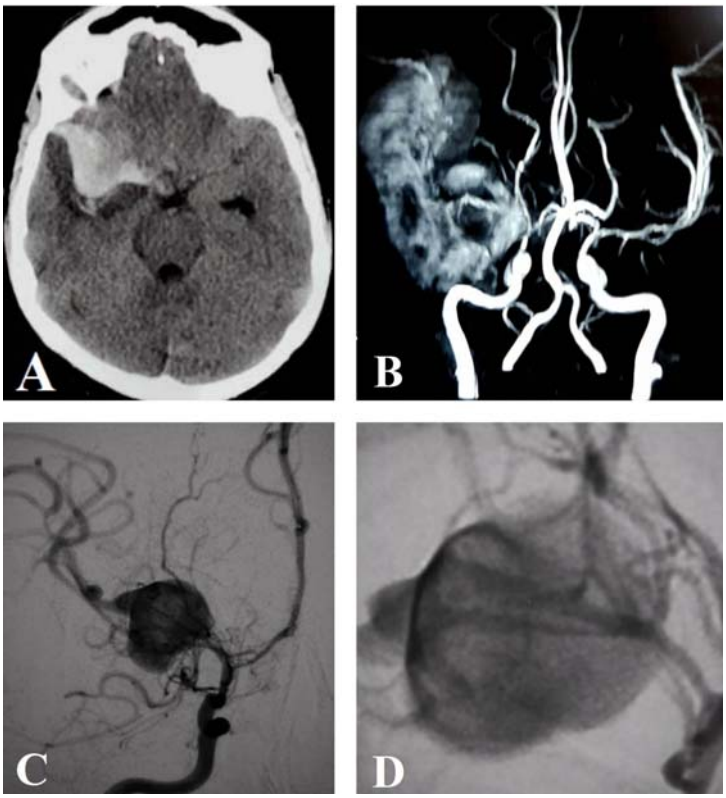
Pictorial CME

Thunderclap headache, beyond subarachnoid haemorrhage

Subhadeep Gupta[1], Arkaprava Chakraborty[1], Deep Das[2], Souvik Dubey[3], Alak Pandit[4], Biman Kanti Ray[4]

19-year-old female presented with acute onset holocranial headache, reached its peak within 1 minute, associated with recurrent vomiting. On examination patient was conscious and alert. Her supine blood pressure was 130/70 mm Hg. Neurological examination was normal except presence of left abducens nerve palsy.

1. What is your diagnosis?
2. Can we suspect the etiology from the parenchymal image only?
3. How do you confirm your diagnosis?
4. What is the best possible management of the patient?



Thunderclap headache is defined as intensely painful headache reaching its peak within seconds to few minutes, often described as the worst headache of life as in our patient. Our patient had thunderclap headache and features of raised intracranial tension as evidenced by left abducens nerve palsy as false localising sign. Possibilities considered were aneurysmal subarachnoid haemorrhage, cerebral sinus thrombosis, cryptococcal meningitis and rarely intracerebral haemorrhage (ICH). Computed tomography scan of brain without contrast (NCCT) shows right temporal bleed (Fig A).

ICH in young can be due to several etiologies including aneurysm, coagulopathies, vascular malformations and rarely intracranial dissections. History of addiction, bleeding diathesis and renovascular & endocrine hypertension were ruled out. Magnetic resonance angiography (MRA) [Fig B] failed to identify underlying pathology as it was largely obscured by blood and proximal right middle cerebral artery (MCA) anatomy was not clear. We decided to perform digital subtraction angiography (DSA) next. DSA [Fig C & D] revealed a dissecting aneurysm involving the entire right M1 segment and distal right internal carotid artery was narrowed. There was good distal flow with the transmural dissection extending till about right M2 segment; there was no extravasation of contrast material.

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Definitive treatment is necessary because it can have 2 possible outcomes. If the dissecting aneurysm gets thrombosed it can cause MCA territory infarctor it may re-rupture leading to significant morbidity and mortality. Ideal treatment in this patient is superficial temporal artery to middle cerebral artery bypass (STA-MCA) where STA is dissected, pushed through a burrhole and anastomosed to a branch of MCA along with sacrifice of the proximal vessel.

Extra-cranial dissections are common in clinical settings but isolated MCA dissection [MCAD] is infrequently reported as a cause of stroke. It is more common in Asian males. Almost 2/3 patients of MCAD have ischemic presentation. DSA is the most effective imaging modality for diagnosis. In 3/4th cases of MCAD, pathology is noted in the M1 segment. Outcome is not favourable in nearly 1/3rd patients of MCAD. These data are taken from a systematic review by Asaithambi G *et al*[1].

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MALARIA

A PRELIMINARY REPORT ON THE STUDIES ON THE ACTION OF 'ABN-61' (A PREPARATION OF DITA-BARK & QUININE) ON CASES OF HUMAN MALARIA

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General Consideration

Malarial fevers are caused by a protozoal parasite belonging to the class Sporozoa, suborder Hæmosporidia, genus plasmodium. There are three main species of malarial parasites which infect man. They include the following:—*Plasmodium vivax* (Grassi & Feletti, 1890) causing benign tertian malaria, *plasmodium falciparum* (Welch, 1897) causing malignant malaria, *plasmodium malariæ* (Laveran, 1881) causing quartan malaria. These species are widely distributed in the tropics. *Plasmodium ovale* (Stephens, 1922) is a rare species and was mainly reported from Africa. It should be noted that besides man, birds and monkeys are also parasitised by various species of plasmodia some of which include the following:—*plasmodium relictum* (præcox) in sparrows, *plasmodium gallinaceum* in fowls, *plasmodium knowlesi* in Simian monkeys.

Inoculation of *plasmodium knowlesi* in man can give rise to fever of mild type with a tendency to spontaneous cure. This species of parasite has recently been introduced for malaria therapy in dementia paralytica (general paralysis of insane). Further, the parasites of bird malaria and monkey (Simian) malaria are being extensively used in the experimental work on malaria.

So far as the human plasmodia are concerned, they pass their life cycle in two different hosts. The one called asexual cycle (Schizogonous) is passed in man (intermediate host) and the other called the sexual cycle (gametocytic) is passed in certain types of female anopheline mosquitoes.

When gametocytes are only found, they indicate that the man is a carrier.

The view that the parthenogenesis of gametocytes may explain the cause of relapse is not accepted. These gametocytes are infective to a female anopheline mosquito and if not taken by these insects they live only for a period of 20 to 40 days, after which they undergo spontaneous degeneration, even without any treatment.

Parasiticidal Action of Quinine

The parasiticidal action of any specific drug depends on the rate of parasitic multiplication and the rate of parasitic destruction. The schizogony cycle of various species of malarial parasites and the number of merozoites formed by each are shown below:—

Plasmodium vivax—16 to 24 merozoites every 48 hours; produces paroxysm every third day; not easily destroyed by quinine.

Plasmodium falciparum—28 to 32 merozoites every 48 hours or under; produces paroxysm every 36 or 48 hours; most influenced by quinine.

Plasmodium malariæ—6 to 12 merozoites events 72 hours; prduces paroxysm every fourth day; refractory to quinine.

The specific action of antimalarial drugs, like quinine and atebrin, brings down the parasitic count of all species of human plasmodia to a sub-clinical level which is unable to cause any febrile paroxysm. These specific drugs also have a destructive action on gametocytes of *pl. vivax* and *pl. malariæ* but are unable to kill the gametocytes of *pl. falciparum*. The only drug which has a destructive action on these gametocytes is 'Plasmochin'.

Relapses are frequent in malarial infections. This is due to the fact that after the fever subsides, the parasites disappear from the peripheral circulation and retire as it were, to some internal organs where they continue to exist. In such a case, the number is insufficient to cause symptoms or to be detected by ordinary laboratory methods of examination. The first relapse usually appears about 3 to 4 weeks after the initial attack has ceased, when the parasite reappears in the peripheral blood. Relapses tend to occur even with specific remedies like quinine and atebrin. Liability to relapse varies with different species of parasites. With *pl. vivax* it has been found to last upto 3 years from the time of the original infection, with *pl.* malariæ upto 6 years; and with *pl. falciparum* upto 9 to 18 months. Relapses occurring after a long interval should be differentiated from cases arising from re-infection, which, however, is not always possible to be verified, or eliminated.

History of Malaria Therapeutics

The parasite of malaria was discovered by the French military surgeon, Alphonse Laveran in 1880 and it took another 18 years when Sir Ronald Ross in 1898 established the mosquito transmission theory. But the treatment of malaria with cinchona bark was known long before the etiology of the disease was discovered. The story of a specific remedy for malaria with quinine starts from the year 1630 when the Countess del Chinchon, wife of a Spanish Viceroy of Peru was cured of 'ague' (malaria) by a native bark. Linnaeus in about the year 1740 named the tree as cinchona in honour of the Countess. The Peruvian bark was subsequently introduced in Europe by the Jesuits in the first half of the 17th century. Later in the first quarter of the 19th century, Pelletier and Cavantou (1820) isolated the principal alkaloid 'quinine' from the cinchona bark. The name 'quinine' is said to be derived from 'quina' the spanish way of spelling the Peruvian word 'kina', that is, bark. For a long time quinine and other allied alkaloids held the field of specific antimalarial therapy.

Researches proceeded on to find out a stronger and better substitute for quinine and it was the last war of 1914-1918 which gave an impetus to German chemists like Professor Schuleman and his colleagues to synthesise a product from methylene blue to supplement the natural alkaloid quinine. It was in September 1926 that they announced a product called 'Plasmochin' and its efficiency was tested by Rohel against bird malaria. 'Plasmochin' was an expensive drug and the hope that it would replace cinchona alkaloids as an antimalarial remedy was not met with great success, because of its feeble action on the

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schizogony cycle of *falciparum*. The only striking effect of this drug which superseded all other antimalarial remedies so far discovered, was its destructive action on the gametocytes of *pl. falciparum* and in this respect it is even superior to quinine. Six years after the discovery of 'Plasmochin' another new compound, also a derivative of methylene blue, 'Atebrin' was obtained by Mauss and Mietzsch. This synthetic product, first named 'Erion' was found effective against bird malaria by Kikuth in 1932. This drug acts powerfully on all species of malarial parasites and compares favourably with quinine, but like the latter drug it is ineffective against gametocytes of *pl. falciparum*. Recently other synthetic antimalarials like Certuna by Kikuth and Cilional by Schuleman have been prepared.

Quinine in Malaria

For over 300 years the alkaloids of cinchona bark were without any competition as specific in malaria and even today. quinine stands as the foremost remedy against malaria. The quinine problem of the province, as well as of India has assumed a great dimension during the present war. The Official Report of 1939 showed that the annual consumption of quinine in India was 210,000 pounds of which, 70,000 pounds were produced locally and for the balance, India had to depend on foreign import. But the annual requirements are really greater. It has been mentioned on a conservative estimate that about 100 million persons in India suffer from malaria in each year and therefore, the annual requirement of quinine for the purpose of effective mass treatment will amount to 1,200,000 pounds (calculating on the basis of 90 grains to each patient), that is, about six times the present yearly consumption. But even then one has to consider the question of relapses. Besides this, whenever there is a possibility of a widespread outbreak of malaria throughout the country (as happened recently during and following famine conditions in Bengal), the amount of quinine requirement will be increased still further.

With limitations of foreign import, the country has to depend mainly on her own production. Although the present production is somewhat over 90,000 pounds and even if the State desires to increase the production of cinchona plantation, it will take a number of years (8 to 10 years) to raise the quinine output so as to make the country self-sufficient. Under the present circumstances the continued demand on quinine as a specific antimalarial remedy when no other specifics like atebrin (mepacrine) and plasmochin (pamaquine) are available, will greatly reduce the quinine stock of India. Some firms have undertaken the manufacture of synthetic antimalarials in India and have achieved a certain amount of success but then again one should remember that there are limitations in this field also, as India has to depend on others for quite a large number of basic chemicals which are imported from foreign countries.. Attempts have, therefore, been made to search for a satisfactory substitute when there are possibilities of the quinine supplies being inadequate to meet the demands of the physician. Experiments were, therefore, conducted in order to get over the difficulty of procuring the requisite quantity of quinine for each case.

Search for an Indigenous Remedy

The possibility of obtaining some indigenous herb which could either replace quinine or even supplement it to a certain extent as an antimalarial remedy was always thought of. Our attention was first directed to *Alstonia scholaris*, popularly known as *chhatim* which enjoyed the reputation of having some antimalarial properties. People of Bengal and of many other parts of India had a great belief in *chhatim* as a febrifuge or antiperiodic and it is a common practice in the Ayurvedic treatment of medicine to prescribe this drug in the form of decoction (*pachan*) for malaria and other febrile conditions. After an extensive investigation with 'dita-bark' it was found that *chhatim* with quinine was as powerful an antimalarial drug as pure quinine itself and it was further observed that whereas a pound of quinine alone could serve only 70 persons (calculating on the basis of disbursement of 100 grains to each person) quinine when mixed with *chhatim* could treat about 200 patients. In this way the quinine requirement may be brought down to one-third of the total requirement of quinine. This preparation was named "ABN-61" and its efficacy as a specific antimalarial remedy was tried in cases of human malaria with great success. Control cases with quinine alone were also observed side by side to find out the amount of quinine required to bring about an effective cure. Although the minimum effective dose of quinine alone is 5 grains three times a day for 6 days, making a total of 90 grains, a greater amount is necessary in a large number of cases and still greater amount should be given to prevent relapses.

If the treatment of malaria is carried out with "ABN-61" the quinine requirement will be greatly reduced and individual cases will only require 12 to 18 grains to control the temperature and 36 to 42 grains of quinine to produce an effective cure. In quinine, the medical practitioners have found a genuine and specific remedy for the disease and have naturally pinned their faith so much as not to fall back upon any other drug when quinine can be procured. But we very well know that the present quinine stock will not be able to supply India's full requirements. From the report of cases (to be published in a later communication) it will be observed that the drug ABN-61 will go a very long way towards the solution of this problem.

Historical Note

The plant Astonia scholaris belongs to the natural order apocynaceæ. Its vernacular names, are Chhatim (Ben.), Saptaparna (Sans.), meaning seven leaf; Chhatim, Datyuni (Hindi).

Rheede (1678) noticed the medicinal use of the bark by the natives along with salt and pepper in febrile dyspepsia. Rumphius (1741) found that the bark was useful in catarrhal dyspepsia and in the febrile states consequent upon that affection and also for enlarged spleen. (Pharmacographia Indica, Vol. 2, 1891). Nimmo (1839) suggested the use of the bark as an antiperiodic. Gibson (1853) described it as antiperiodic.

In a report on the centennial exhibitions, presented to the American Pharmaceutical Associations (Transactions, 1877), it was stated that equal doses of ditain (obtained from dita-bark) and sulphate of quinine had the same medicinal effects while ditaine is free from any disagreeable secondary symptoms which were usual concomitants of large doses of quinine. The results arrived at with the alkaloid of dita-bark in Manila hospitals and also in private practice were simply marvellous. It was being employed with most satisfactory results in the Islands of Mindanao where malignant fevers were prevalent (quoted from Watt's 'A dictionary of economical products of India, Vol. I,

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1898). Cathcart (1879) in the *American Journal of Pharmacology* stated that 'the bitter bark of *Alstonia constricta* (the Australian species), sometimes called the native quinine, is in common use by the shepherds in the interior of Southern Australia as a domestic remedy for malarial fevers'. Stille and Maisch (1896) reported that the dita-bark and its alkaloid was used successfully in intermittent fever in the East Indies.

The first report of Proceedings of Central Indigenous Drugs Committee of India (published, Calcutta 1901) showed that *A. scholaris* had some febrifuge effect which was not lasting. Stewart used it in one drachm doses and reported that in mild cases of fever it was as effective as quinine. Nailer (1901) used the drug in 14 cases of "ague" in Tanjore (Madras) and found that in all cases it caused the temperature to fall steadily in a short time; no persipration was induced but the urine was observed to be increased and high coloured (quoted from Kirtikar and Basu's Indian Medicinal Plants, 1911).

Goodson, Henry and Macfi (1930) studied the activities of *A. scholaris* and *A. constricta* on bird malaria and found that echitamine (alkaloid of *A. scholaris*) had only a feeble action in doses of 5 mgm.

Buttle (as reported by Sharp, 1934) showed the inactivity of alstonian sulphate in bird malaria.

Mukherji, Ghosh and Siddons (1942) used a 1 to 2 per cent solution of the sulphate of total alkaloids of *Alstonia scholaris* as an intramuscular injection in doses of 20 mgm. per kilo body weight in cases of induced malaria (*plasmodium knowlesi*) in monkeys. They observed that the drug failed either to retard or to control the progress of infection. Later, they prepared a tincture(1 in 10) from the powdered bark containing 1·3 grs. of total alkaloid per ounce. This was administered in doses of one ounce thrice daily in a number of cases of human malaria of which one was of *pl. vivax* infection and three of *pl. falciparum* infections. They found that the drug had no demonstrable antimalarial action as it did not produce any remarkable febrifugal effect or alter in any significant way the course of infection.

From the above it will be found that the drug was found to be highly satisfactory by earlier workers while subsequent observations mostly applied on bird malaria and monkey malaria tend to prove the inefficacy of the drug in malaria infections. Such were the conflicting reports on the antimalarial property of *Alstonia scholaris*.

Present Observations with Aisotonia Scholaris

A series of preparations were made from dita-bark alone which were used in cases of human malaria. In the earlier works a very satisfactory result was not obtained as hoped for. In some cases, however, a beneficial effect by the administration of pure *chhatim* (dita-bark) was observed in that it either delayed the onset of the next paroxysm or reduced the duration of the next paroxysm. Daily examination of the blood showed that in earlier phases of infection the drug lowered the parasite count but could not retard the progress of infection. Later, a preparation was made in the form of tablet with *chhatim* (dita-bark) and quinine which was named 'ABN-61". This latter drug was then experimented on a series of cases of human malaria and found to be very effective. Case no. 1 shows that 14 tablets of AB-7 (preparation of dita-bark only) could not control the temperature while 10 tablets of ABN-61 (preparation of dita-bark and quinine) had a definite effect on the temperature and parasite count.

"ABN-61" as an Antimalarial Remedy—The therapeutic action of any antimalarial drug is usually first tested on either bird malaria or monkey malaria and then finally applied on human malria. It is quite resonable that before a drug is applied on human cases, a preliminary biological test on animals is necessary to select only those drugs which give indications for further study. The present observation was, however, directed mainly

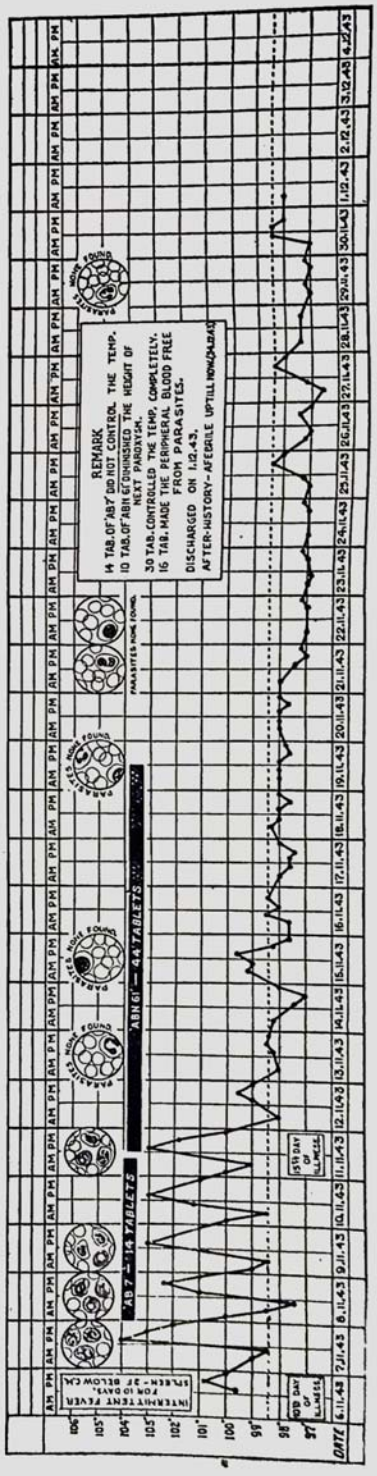

Chart of a case of benign tertian malaria (case no. 1) showing quotidian type of temperature. Two generations of *plasmodium vivax* multiplying on alternate days. Circular diagrams on the top show the forms of parasites as found in the peripheral blood examined by thin film method. AB 7—Tablets of *Chhatim* only. ABN-61—Tablets of *Chhatim* and Quinine.

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against human malaria and the investigation was conducted on patients admitted in the Carmichael Medical College Hospitals, Belegachia (Calcutta).

Dosage and Method of Administration—The general method followed was to administer 2 tablets of "ABN-61" three times a day to adult persons for a period of at least six days. The tablets were given orally and were swallowed with the aid of drinking water or the crushed tablets were dissolved in water before being taken. No other accessory treatment was introduced except the administration of alkali mixture and intravenous glucose in certain cases. The final dosage of "ABN-61" and the course of treatment was altered in some cases which were, however, guided by the nature of the effect observed on temperature and parasite count. In children the dose of "ABN-61" was modified accordingly. Each tablet of "ABN-61" contained only 1 grain of quinine and the total requirement to cure an attack was about 36 to 42 grains given in the course of 6 to 7 days.

Experimental Method—The methods of observation followed in the present series were to confirm all cases of clinically diagnosed malaria, *i.e.*, cases of sudden onset of fever with chill and rigor associated with or without enlargement of the spleen, by finding the malarial parasite from a microscopical examination of thin blood film. The drug was administered only in those cases which revealed the presence of malaria parasite. Further in every case where the parasite was detected in the peripheral blood, the patient was allowed to have the malarial paroxysm while in the hospital and then the treatment was commenced. During the period while the drug was withheld a simple alkaline mixture was only given. All the cases in which the drug "ABN-61" was tried had no history of taking quinine prior to admission in the hospital. After the drug was administered particular attention was paid regarding its effect in controlling the temperature, its destructive effect on asexual and sexual forms of the parasite, the time taken to make the peripheral blood from parasites, its effect on enlarged spleen and any untoward effect resulting from its administration. The parasiticidal action was observed by making a parasite count before the drug was commenced and then daily during the course of treatment. After the drug was discontinued, the blood was examined occasionally to check whether there was any reappearance of the parasite in the peripheral blood. Before the patient was discharged from the hospital, the blood was again thoroughly examined for parasites both by thin and thick film methods. Those cases who showed crescents (gametocytes of *pl. falciparum*) were not discharged from the hospital till the crescents disappeared. These forms of parasite are resistant even to quinine but can be destroyed by plasmochin. But in the present observation no further treatment was given and the crescents showed a spontaneous degeneration and gradual decrease in number till they finally disappeared. As the gametocytes are formed from the asexual forms, it is evident that the destruction of the latter will eventually lead to the disappearance of the former from the peripheral blood. To study the effect of the drug on the incidence of relapse, the patient was kept under observation in the hospital for a period of one fortnight to three weeks from the time of cessation of temperature. The cases were then followed up by instructing the patient to intimate any rise of temperature and further to submit a weekly report of the temperature.

Summary of the Results of Observation—The criterion of cure in malaria with any specific antimalarials is judged from its effect in controlling the temperature, causing the disappearance of the parasite from the peripheral blood and preventing the occurrence of relapses or lowering the incidence of relapse rate. Results obtained by treating cases of human malaria with the drug "ABN-61" so far fulfils all the above criteria. The present investigation on human malaria showed that 12 to 18 tablets of "ABN-61" administered in the course of 2 to 3 days were required to control the temperature and another 6 to 12 tablets were necessary to make the peripheral blood free from parasites. Excepting the gametocytes of *plasmodium falciparum*, the drug was found to have a powerful destructive effect on all species of malarial parasites which infect man. The drug had a definite inhibitory effect on the schizogony cycle. Daily examination of the blood during treatment showed a striking reduction in the number of parasites. In some cases a clear evidence of degeneration of parasites was obtained. The drug, therefore, exerted some physical effects of varying degrees and altered the morphological appearance of the parasite.

Conclusion

The present study justifies the recommendation of "ABN-61" as a safe antimalarial remedy as it was found to have marked parasiticidal action on all species of malarial parasites with the exception of the gametocytes of *plasmodium falciparum*. Further, while under the treatment of "ABN-61" the patient did not complain of any disagreeable symptoms (tinnitus and deafness) as are associated with cases treated with effective therapeutic doses of quinine (varying from 45 to 90 grains or more). This is, therefore, a distinct advantage over quinine. In the present series of cases no idiosyncrasy to the drug has yet been observed.

Acknowledgment

Our thanks are due to Messrs. Gluconate Ltd. who have helped us considerably in carrying out this investigation. The tablets ABN-61 and other tablets of *chhatim* only and also of *chhatim* and quinine as required for the present investigation were prepared by the same firm and were supplied to us free of cost.

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Comments from Expert : After 75 years

Malaria in India with Special Reference to Severe *Vivax* Malaria

Dhanpat Kumar Kochar[1], Abhishek Kochar[2]

P vivax **remains a substantial health problem and economic burden in India with proven difficulties to control it, particularly in urban areas. Although number of malaria cases in India has declined in the recent years, the relative proportions of *P. vivax* cases are increasing. *P. vivax* is transmitted by a variety of vectors across diverse ecological habitats and shows polymorphism in the pattern of relapse. It can also be overlooked as a pathogen when a mixed infection with *P. falciparum* is present. During last two decades, there is substantial evidence that *P. vivax* is associated with all sort of severe manifestations including cerebral malaria and death in India. This may be because of improved diagnostic facilities, reporting, investigation and/ or changes in *P. vivax* pathogenicity, which may be specific to individual parasite populations in different areas. As there is heterogeneity in transmission intensities of the *P. vivax*, there is tremendous scope for research in India for studying the parasite biology detection and treatment of hypnozoites to ensure radical cure.**

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Key words **: Anopheles mosquito, Severe Vivax Malaria, Chloroquin, Artesunate.**

Malaria is a vector-borne parasitic tropical disease found in 91 countries worldwide caused by *Plasmodium falciparum, Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale, and Plasmodium knowlesi*. It is transmitted by the bite of the female *Anopheles* mosquito. The disease incidence depends on environmental suitability for local vectors in terms of altitude, climate, vegetation, and implementation of control measures, and is linked to poverty, natural disasters, and war. *Plasmodium falciparum* and *P vivax* are the predominant species worldwide. The great majority of *falciparum* malaria occurs in sub-saharan Africa whereas *P. vivax* malaria is much less common because the population in this region is Duffy antigen negative. *P. vivax* malaria is common in Southeast Asia including India and America. *P malariae* and *P ovale* have a global distribution, however *P knowlesi* is predominantly seen in Malaysia, and adjacent southeast Asian countries[1].

Indian population is having a great burden of malaria cases because an estimated 95% population lives in areas where climatic conditions favour malaria transmission[2]. Whole India is endemic for malaria, except hilly areas of 2000 m above sea level where the mosquito is scarce due to unfavourable climatic condition. The presentation of malaria in India is very complex and the ratio of *P. vivax* and *P. falciparum* varies from place to place across the India. Few states like Orissa, U.P., Gujarat, West Bengal, Maharashtra, Madhya Pradesh, Rajasthan, Karnataka and Andhra Pradesh are highly endemic for malaria and contribute 90% of the total malaria cases in the country[3]. Malaria epidemiology in North-eastern states of India is complex due to high aboriginal population, varied terrain, rich forest cover and favourable climatic conditions for vector growth and malaria transmission[4]. However, alpine environment in Arunachal Pradesh and Nagaland, high proportions of *P. vivax* cases (60-80%) have been reported, while in Manipur, *P. vivax* contribute 42 – 67% and in Assam with subtropical to tropical climate it varies from 23-31 per cent. Meghalaya, Tripura and Mizoram are consistently having the lowest population of *P. vivax* cases over several years. Because of rapid construction, migration, and the

Editor's Comment :

- **Investigation of Malaria in any state any time in a case of Acute febrile illness is highly relevant.**
- **Malaria is changing its character - benign vivax malaria is not at all benign.**
- **There is upsurge of drug resistance Malaria.**
- **Early diagnosis and prompt therapy and ahereness is key to prevent resistance.**

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mushrooming of slums in the urban setting of India malaria particularly *P. vivax* control is very troublesome.

Mosquito Vectors :

Although multiple vector species may be present in any specific region, there is no single vector species which is found all over India. *Anopheles culicifacies* is responsible for an estimated 65% of malaria in India as this is the main malaria vector in rural, peri-urban areas, and in the plains. This species is mostly zoophagic and breeds in plain-land ecosystem. *A. stephensi* is also primarily zoophagic and an important vector for malaria in urban areas. It prefers human hosts in the absence of cattle. In the forest areas of North-eastern regions, *A. dirus* is an efficient vector which breeds in temporary water collections. It is exophagic and exophilic by nature. *A. minimus* is another vector in the forest areas of North-eastern regions, which is breeding in slow-flowing streams and exhibiting zoophilic and exophilic behavior. Another species responsible for perennial transmission in hill and foothill areas of central and Southern India is *A. fluviatilis*.

Biology :

The life cycle of parasite is completed in human and mosquito. The sporozoites are inoculated in humans by the bite of an infected female *Anopheles* mosquito. The parasite undergoes a pre-erythrocytic liver stage lasting for 1–2 weeks before the onset of the blood stage, where serial cycles of asexual replication produce increased number of parasite causing fever. A subpopulation of intraerythrocytic parasites switches to sexual development, producing female and male gametocytes, which are taken by mosquito via a blood meal. After a series of changes in mosquito the oocyst releases sporozoites which migrate to the mosquito salivary glands, completing the lifecycle. In *P. vivax* and *P. ovale* infections, a proportion of sporozoites become dormant hypnozoites, capable of producing relapses even after months or years of initial infection.[5]

Pathogenesis :

Usual incubation periods is around 10–18 days depending of different species, however, some strains of *P vivax* have a 3–6 month primary incubation period. The classical periodic fever with spikes occurs at fixed interval corresponding to the erythrocytic cycle length of the infecting species (24 h for *P. knowlesi*, 48 h for *P falciparum*, *vivax*, or *ovale* and 72 h for *P malariae*), but such patterns are rarely observed these days. In *P. falciparum* infection, the parasitized RBCs sequester inside small and medium sized vessels, avoiding parasite clearance in the spleen and causing host endothelial cell injury and microvascular obstruction. Cytoadherence is mediated by *P falciparum* erythrocyte membrane protein 1 (PfEMP1), which binds to different endothelial receptors; for example, intercellular adhesion molecule–1 and endothelial protein C receptor are associated with cerebral malaria. Parasitized RBC also binds to uninfected cells (rosetting), and they become rigid and less deformable, exacerbating microvascular obstruction. In the brain, it produces additional hypoxic injury through release of nitric oxide (NO) leading to coma and convulsion, in the lungs it predisposes to respiratory failure and ARDS. In pregnant women, sequestration in the intervillous space of the placenta leads to placental malaria causing of maternal anaemia, low birth weight, preterm labour, and increased risk of abortion and stillbirth. Placental cytoadherence is mediated by binding to chondroitin sulphate A (CSA), and the effects are most severe in primigravid women. Anaemia is a common feature of malaria and is typically multifactorial in origin including intravascular haemolysis, bone marrow suppression and dyserythropoiesis.[5,6]

Clinical presentation :

Malaria is described conveniently as uncomplicated and severe malaria. Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity or continuous and may be associated with chills and rigors. The fever is often accompanied by headache, myalgia, arthralgia, anorexia, nausea and vomiting. The symptoms of malaria can be non-specific and mimic other diseases like viral infections, enteric fever etc. Severe malaria is an emergency and manifestations can develop over a span of time as short as 12 – 24 hours and may lead to death. Severe malaria has specific diagnostic criteria which includes the most common manifestations of different organ dysfunction.

The important clinical and laboratory criteria for defining severe malaria are impaired consciousness or unrousable coma, prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance, failure to feed, multiple convulsions – more than two episodes in 24 h, deep breathing, respiratory distress (acidotic breathing), circulatory

collapse or shock, systolic blood pressure < 70 mm Hg in adults, and < 50 mm Hg in children, clinical jaundice plus evidence of other vital organ dysfunction, haemoglobinuria, anuria or oliguria, abnormal spontaneous bleeding, pulmonary oedema (radiological). The laboratory parameters includes hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl), metabolic acidosis (plasma bicarbonate < 15 mmol/l), severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%), haemoglobinuria, hyperparasitaemia (> 2%/100 000/ìl in low intensity transmission areas or > 5% or 250 000/ìl in areas of high stable malaria transmission intensity), hyperlactataemia (lactate > 5 mmol/l), renal impairment (serum creatinine > 3mg%).

Characteristic fundoscopic findings in cerebral malaria include retinal whitening, changes in blood vessel contour, haemorrhages and papilloedema. These changes have direct correlation to the severity of disease. Neuroimaging typically shows some evidence of brain swelling but this is less prominent in adults than in children, in whom brain swelling is strongly associated with a fatal outcome. Foetal and maternal complications are more common in pregnancy with severe malaria; therefore, they need prompt attention.[7,8]

Complications of malaria :

The neurologic sequelae (Post malaria neurological syndrome) in the form of psychosis, cerebellar ataxia, cranial nerve involvement, hemiplegia and aphasia may be seen after recovery from coma but are usually self limiting. Other long term neurological complications following an episode of cerebral malaria may cause permanent visual, motor deficits, learning disorders and epilepsy. Haematological complications of malaria include hyper-reactive malarial splenomegaly (HMS), and rarely, splenic rupture. *P. malariae* can cause anaemia and nephrotic syndrome. Delayed haemolytic anaemia can occur after artemisinin treatment in some persons. The key event appears to be pitting, a splenic process whereby ring-stage parasites killed by artesunate are expelled from their host erythrocytes which return to the circulation, but with a reduced lifespan.[9,10]

Status of *vivax* malaria: Benign to Severe :

Until the beginning of this century, it was believed and preached that most serious and life- threatening complications of malaria are caused only by *P. falciparum* infection, whereas *P. vivax* infections are relatively mild, and runs a benign course and does not require hospitalization[11,12,13]. However, the dominant paradigm of *P. vivax* being a benign infection has been challenged recently from India. First authentic report of severe *vivax* malaria in world literature came in 2004 from Bikaner, India, when Kochar et al. reported that both sequestration and non–sequestration related complications like cerebral malaria, renal failure, circulatory collapse, convulsion, severe anemia, thrombocytopenia with or without bleeding, hemoglobinuria, abnormal bleeding, acute respiratory distress syndrome (ARDS), hepatic dysfunction, jaundice, and pregnancy-related complications including intrauterine growth restriction (IUGR) and miscarriage can be caused in patients suffering with *P. vivax* malaria. Two out of 11 patients died and one developed postmalarial psychosis. Polymerase chain reaction (PCR) test was used to confirm the diagnosis of *P. vivax* as well as to rule out *P. falciparum* coinfection.[14] Since then, similar reports are coming from all over India (Table 1). In many of these studies, the authors have used stringent test to exclude *falciparum* malaria and other coinfection. There is substantial variation in the reported geographic distribution and the incidence of severe manifestations of *vivax* malaria in different parts of India.

Recently, there are several reports of severe *vivax* malaria from other countries like: Thailand, Brazil, Indonesia, Papua New Guinea (PNG), and many other Asian and African countries including autopsy confirmation.[15,16] The occurrence of severe symptoms seems to be more frequent among females, pregnant women, individuals presenting with their first malarial infection, and those with other acute or chronic illnesses. In a joint collaborative multinational study, the overall case fatality was about 20-fold higher in India as compared to Brazil, and therefore highlighting the variability observed in different settings.[11] Recent evidences suggest that *vivax* malaria had almost similar risk of developing severe malaria, multiorgan dysfunction, and mortality as seen with *P. falciparum* infection.[17] The occurrence, relation, and magnitude of thrombocytopenia is also more in *P. vivax* of malaria.[18,19] There are several possible explanations for this observation which includes possibility of a longer liver stage of *P. vivax* allowing prolonged periods

for the parasite to remain in host environment, even if transmission is interrupted and the primary infection has been treated successfully.

Diagnosis :

The diagnosis of malaria is essentially clinical and is confirmed by the demonstration of presence of parasites in the peripheral smear or parasite-derived proteins by RDTs. Microscopy of stained thick and thin peripheral blood smear (PBF) remains the gold standard for confirmation of malaria. It is cost-effective, fairly sensitive and highly specific. It helps in knowing the exact species and quantification of parasites, and also in assessing response to antimalarial treatment. Microscopic evidence may be negative for asexual parasites in the some patients of severe malaria due to sequestration and partial treatment. Efforts should be made to confirm these cases by RDT or repeat microscopy. However, if the symptoms clearly point to severe malaria and there is no alternative explanation, such a case should be treated accordingly. RDTs are based on the detection of circulating parasite antigen in whole blood. These tests are fairly sensitive and specific and can be done in the field situation. These tests are good to study the species but not for quantification of parasites. The hidden sequestered biomass in severe malaria can be estimated from PfHRP2 concentrations in plasma. However, RDTs using monoclonal antibodies against parasite Lactate dehydrogenase (Optimal) may be very useful. Quantitative buffy coat (QBC) test using fluorescent dye and PCR can also be used for the diagnosis. The sensitivity of PCR assay is very high, and it can detect even 1 parasite/mL of the blood. Other diagnostic technique include loop- mediated isothermal amplification (LAMP), microarrays, automated flow cytometry (FCM), automated blood cell count (ACC), ultraviolet laser desorption mass spectrometry (LDMS), enzyme-linked immunosorbent assay (ELISA)/ enzyme immunoassay (EIA), latex agglutination assay, and cultivation of live malaria parasites.

Managent of Malaria :

The Early diagnosis and prompt treatment of malaria aims at complete cure, prevention of progression of uncomplicated malaria to severe disease, prevention of death, interruption of transmission, minimizing risk of selection and spread of drug resistant parasites.

The *P. vivax* is highly sensitive to chloroquine in India and resistance to it is not reported in general. Treatment of parasitologically, confirmed cases of uncomplicated cases of *P. vivax* malaria in India requires administration of 3 day course of oral chloroquine (25 mg/kg) for treatment of acute blood stage infection along with 14-day course of oral primaquine (0.25 mg/kg) to treat the dormant hypnozoites stage (radical cure). Primaquine should not be used in infants, pregnant women, and individuals with glucose- 6-phosphate dehydrogenase (G6PD) deficiency. As G6PD deficiency testing is not routinely available in the field, the patients are instructed to stop primaquine treatment and report back to the health care facility in case of dark urine or hematuria and cyanosis or blue coloration of the lips. As per recommendation of treatment of malaria in India, severe *P. vivax* malaria should be treated similar to severe *P. falciparum* malaria along with 14 days primaquine therapy.[7,8,20]

As an alternative of primaquine, recently United States Food and Drug Administration has approved, tafenoquine 300 mg single dose for the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection. This approval is an important step forward, as a new, single dose treatment for relapsing malaria[21].

Artemisinine combination therapy (ACT) is the treatment of choice for *P. falciparum* uncomplicated malaria. ACTs consist of a combination of an artemisinin derivative that rapidly reduces parasitaemia and a partner drug that removes residual parasites over a longer period. The leading ACTs in use are artemether–lumefantrine, artesunate–amodiaquine, dihydro-artemisinin–piperaquine, artesunate–mefloquine, and artesunate plus sulfadoxine–pyrimethamine. Artemether–lumefantrine should be given with milk or food containing fat to enhance lumefantrine absorption. In endemic areas, prescription of a single dose of primaquine (0·25 mg/kg) with an ACT is recommended to reduce the risk of onward transmission. This dose is considered safe in G6PD deficiency.

Severe malaria caused by *P. falciparum*, *P. vivax* and mixed infection is a medical emergency and should be treated urgently and preferably in the intensive care unit. The principles of management include specific antimalarial drug treatment, care of the unconscious patient, symptomatic treatment and

treatment of associated complications. Specific antimalarial therapy should be started immediately even on the basis of clinical diagnosis if parasitological confirmation is likely to be delayed.

Artesunate should be administered in the dose of 2.4 mg/kg bodyweight IV on admission, at 12 and 24 h, and then once a day for 7 days. Alternatively, artemether or artether can be used parenterally. Once patients can tolerate oral therapy, they should receive complete dosage of artemisinin-based combination therapy (ACT) for 3 days. Alternatively, quinine is given as loading dose of 20 mg/kg to be diluted in glucose or glucose normal saline followed by 10 mg/kg bodyweight every 8 h, and the infusion should take a minimum of 4 h. Later on, the treatment should be switched to oral therapy to complete the 7 days of treatment along with doxycycline (3 mg/kg once daily) or clindamycin (10 mg/kg twice daily), except for pregnant women and children younger than 8 years of age for whom doxycycline is contraindicated. The loading dose of quinine is not given if the patient has taken oral quinine or mefloquine in the previous 24 h. The dose of quinine is reduced to 5–7 mg/kg bodyweight if IV therapy is continued after 48 h. The dose of artemisinin does not require any adjustment.

Severe malaria often causes multiorgan dysfunction and the presence of these complications influences the patient's overall outcome and requires vigorous and meticulous treatment simultaneously. The hyperpyrexia is treated by tepid sponging and paracetamol. Convulsions are treated by intravenous lorazepam followed by loading dose of phenytoin or fosphenytoin. Convulsive status should be treated with usual protocols. Hypoglycaemia is very common in children and pregnant women and should be treated by IV 25–50% glucose. Usually, hypoglycaemia responds well to standard therapy, although hyperinsulinaemic hypoglycaemia in association with quinine therapy responds well to long-acting somatostatin analogues. Blood transfusion is generally recommended if the haemoglobin level is less than 5 g/100 mL (haematocrit less than 15%). In acute renal failure or severe metabolic acidosis, haemofiltration or haemodialysis should be started early. The fluid balance is critical in severe malaria because of narrow window between overhydration (pulmonary oedema) and under hydration (exacerbation of renal impairment and tissue hypoperfusion). Pulmonary oedema is treated by avoiding excessive rehydration and use of oxygen, whereas over hydration requires stopping IV fluids and use of a diuretic (furosemide: 40 mg IV) along with withdrawing 3 mL/kg of the blood by venesection into a donor bag. Circulatory collapse, shock and algid malaria are treated by parenteral antimicrobials and vasopressors, along with correction of haemodynamic disturbances. Bleeding and DIC requires transfusion of fresh blood or clotting factors, along with vitamin K (10 mg IV). Bleeding associated with marked thrombocytopenia may require platelet transfusion. Hyperparasitaemia (greater than 20%) should be treated by exchange transfusion. A close monitoring of pregnant women is essential because of high incidence of pulmonary oedema and hypoglycaemia. Parenteral artesunate is preferred in the second and third trimesters, whereas quinine is the drug of choice in the first trimester. Single dose of primaquine in *P. falciparum* infection and 14 days primaquine treatment in *P. vivax* and mixed infection should follow for treatment of gametocytes.[8,20]

Adjunctive Therapy :

Despite highly effective primary therapy against the parasite (quinine and artesunate), mortality and morbidity from cerebral malaria remains very high. Adjunctive therapies administered in the meantime might reduce the risk of mortality and neurocognitive sequelae in view of the fact that antimalarial drugs often take at least 12–18 h to kill the parasites. New therapies being considered as adjunctive therapy in cerebral malaria include reduction of iron burden (desferoxamine, deferiprone), anticoagulation (heparin), inhibition of cytoadherence (PfEMP-1 antagonists, levamisole, N -acetylcysteine and atorvastatin), Rho-kinase inhibition (fasudil), endothelium fixing drugs (NO and l -arginine), immune modulation (dexamethasone, immunoglobulins, anti–TNF monoclonal antibodies, pentoxifylline, rosiglitazone and curcumin), neuroprotection (erythropoietin) and correction of acidosis (dichloroacetate and N–acetylcystained). A number of agents have been or are being tested, but none has shown unequivocal evidence of improvement in clinical trials. Consequently, none of these agents can be recommended as part of the standard management strategy at present. Albumin is the only adjunctive therapy associated with reduced mortality in children. Among other agents, levamisole and arginine may be the most promising, based on

preliminary studies, but no large trials have yet been completed.[22,23]

Vaccine development :

A malaria vaccine, deployed in combination with current malaria control tools, could play an important role in future control and eventual elimination of malaria. Despite more than a century of extensive research, only one malaria vaccine candidate (RTS,S/AS01) has approval for use in countries where malaria is endemic. It provides significant protection against *falciparum* malaria infection over a 3–4 year period in older children. However, efficacy was relatively lower in very young children (6–12 weeks old). An overall reduction in long-term mortality remains to be demonstrated. A contrasting approach to producing sporozoite-based immunity is the *P falciparum* sporozoite (PfSPZ) vaccine, an intravenous injection of irradiation-attenuated sporozoites. PfSPZ has now entered clinical trials in Africa; Transmission-blocking vaccines against sexual-stage antigens have also been tried but till date no effective vaccine is available.[24,25]

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Severe *vivax* malaria in India

Sl. No	Author	No. of Patients	Major Complication in Adult / Child	PCR confirmed	doi / PMID
1	Kumar R et al - 2020 from Manipal	122	Jaundice, Renal failure, Anemia	–	PMID: 28367735 PMCID: DOI: 10.1080/20477724.2017.1309342
2	Anvikar et al – 2020 from Gujarat	30	Jaundice	PCR Confirmed	PMID: 32490754 DOI: 10.1080/21505594.2020.1773107
3	Methews et al – 2019 from Delhi	150	Thrombocytopenia, Jaundice, ARDS, Spontaneous bleeding, Metabolic acidosis, Shock, Renal Failure, Cerebral Malaria (Adult)	–	PMID: 31579662 DOI: 10.4103/tp.TP_2_19
4	Mukhtar et al – 2019 from Sudan	1	Cerebral Malaria (Adult)	–	PMID: 31533821 DOI: 10.1186/s12936-019-2961-1
5	Akhlaq et al – 2018 from Karachi	7	Cerebral Malaria	–	PMID: 30191906 DOI: 10.4997/JRCPE.2018.302
6	Kochar et al – 2017 from Bikaner	1	Cerebral Infarct (Adult)	PCR confirmed	PMID:28748845
7	Kumar R et al – 2017 from Manipal	511	Hyperbilirubinemia, ARDS, AKI, Cererbral malaria (Adult)	PCR confirmed	10.1080/20477724.2017.1309342 PMID:28367735
8	Kumar P et al – 2017 from New Delhi	1	Peripheral Gangrene (Adult)	-	10.4103/ijccm.IJCCM_424_16 PMID:28515614
9	Kochar et al – 2016 from Bikaner	150	Retinopathy (Adult)	PCR confirmed	doi: 10.1080/20477724.2016.1213948 PMCID: PMC5072115
10	Jain et al – 2016 from Dehradun	48	Hepatopathy (Adult)	-	10.1016/j.actatropica.2016.03.031.
11	Mallela et al – 2016 from Manipal	1	Subdural haemorrhage with severe thrombocytopenia (Adult)	-	10.7860/JCDR/2016/15418.7098
12	Gupta et al – 2016 from New Delhi	12	Anemia with thrombocytopenia (Adult)	-	10.1016/j.meegid.2016.02.014
13	Sequiera AM, Lacerda M, Kochar DK et al – 2015 from Bikaner	462	Anemia, jaundice, renal failure, cerebral malaria, death (Adult)	PCR Confirmed	10.1186/s12916-015-0302-y
14	Mitra et al – 2015 from Vellore	83	Thrombocytopenia and hyperbilirubinemia (Adult)	-	PMID: 26714506
15	Gupta et al – 2015 from Manipal	1	ARDS (Adult)	-	10.3855/jidc.6813
16	Kochar et al – 2014 from Bikaner	221	Hepatic dysfunction, thrombo-cytopenia, anemia, cerebral malaria, MODS, death (Adult)	PCR Confirmed	PMID: 25253213
17	Kumar et al – 2014 from Jaipur	1	Renal cortical necrosis (Adult)	-	10.4103/0971-4065.133789
18	Dev et al – 2014 from Faridabad	1	Myocarditis and heart failure (Adult)	-	PMID: 25467272
19	Muley et al – 2014 from Vadodara	66	Thrombocytopenia (Adult)	-	10.1155/2014/567469
20	Mittal et al – 2014 from Delhi	64	Severe anemia (Child)	-	PMID: 24947218
21	Nandwani et al – 2014 from Meerut	110	Acute kidney injury, jaundice, severe anemia (Adult)	-	10.1007/s12639-012-0208-y
22	Nayak et al – 2013 from Bikaner	5	Cardiovascular involvement (Adult)	PCR confirmed	PMID:24717201
23	Singh et al – 2013 from Chandigarh	19	Jaundice with hepatic dysfunction (Adult)	-	10.1155/2013/341862
24	Singh et al – 2013 from Dehradun	61	Thrombocytopenia (Adult & Child)	-	10.7860/JCDR/2013/6914.3479
25	Jain et al – 2013 from Jabalpur	22	Cerebral malaria, seizures, severe anaemia, and respiratory distress (Adult)	PCR confirmed	10.1179/204777213X13777615588180

Sl. No	Author	No. of Patients	Major Complication in Adult / Child	PCR confirmed	doi / PMID
26	Sharma et al – 2013 from New Delhi	54	Severe thrombocytopaenia jaundice with deranged LFT values (Child)	-	10.7860/JCDR/2013/5633.3370
27	Rizvi et al – 2013 from Alighar	62	Hepatic and renal dysfunction (Adult)	-	10.4103/1596-3519.117624
28	Sarkar et al – 2013 from Darjeeling	200	Jaundice (Adult)	-	10.4103/2229-5070.113912
29	Tanwar et al – 2012 from Bikaner	278	Thrombocytopenia (Child)	-	10.3109/09537104.2011.607520
30	Limaye et al – 2012 from Mumbai	50	Thrombocytopenia (Adult)	-	PMID: 23777019
31	Agarwal et al – 2012 from Rohtak	1	Multiple splenic infarct (Adult)	-	10.1016/S1995-7645(13)60051-6
32	Kaushik et al – 2012 from Dehradun	63	AKD (Adult)	-	10.1093/trstmh/trs092
33	Sharma et al – 2012 from New Delhi	46	Severe anemia and thrombocytopenia (Child)	-	10.1179/2046905512Y.0000000012
34	Kute et al – 2012 from Ahmedabad	1	Renal acute cortical necrosis and acute kidney injury (Adult)	-	10.1007/s00436-012-2975-x
35	Yadav et al – 2012 from New Delhi	131	Hepatic, renal and respiratory disease (Child)	-	10.1007/s12098-011-0603-x
36	Tanwar et al – 2011 from Bikaner	13	Cerebral malaria (Child)	PCR confirmed	10.1179/1465328111Y.0000000040
37	Kochar et al – 2010 from Bikaner	143	Thrombocytopenia (Adult)	PCR Confirmed	10.3109/09537104.2010.505308
38	Kochar et al – 2010 from Bikaner	65	Hepatic dysfunction, thrombocytopenia, anemia, cerebral malaria, renal failure, MODS, death (Adult)	PCR Confirmed	10.4269/ajtmh.2010.09-0633
39	Sarkar et al – 2010 from Kolkata	3	ARDS (Adult & Child)	-	10.4103/0970-2113.68323
40	Kochar et al – 2009 from Bikaner	40	Jaundice, renal failure, anemia, thrombocytopenia, MODS, death (Adult)	PCR confirmed	PMID: 19190212
41	Parakh et al – 2009 from Delhi	3	Cerebral malaria and severe anemia (Child)	-	10.1179/027249309X12547917868844
42	Thapa et al – 2009 from Kolkata	1	Severe thrombocytopenia with severe bleeding (Child)	-	10.1097/MPH.0b013e3181b7eb12
43	Harish et al – 2009 from Jammu	2	Thrombocytopenia and cerebral complication (Child)	-	10.1007/s12098-009-0087-0
44	Harish et al – 2009 from Jammu	2	Severe thrombocytopenia and cerebral malaria (Child)	-	10.1007/s12098-009-0087-0
45	Sarkar et al – 2008 from Varanasi	3	Cerebral malaria (Adult)	-	10.4103/0972-5229.45084
46	Kochar et al – 2007 from Bikaner	1	cerebral malaria in status epilepticus (Adult)	PCR confirmed	10.1016/S0140-6736(07)61417-2
47	Kaur et al al – 2007 from Delhi	1	Severe thrombocytopenia with acute renal failure (Child)	-	PMID: 17264156
48	Kochar et al – 2005 from Bikaner	11	cerebral malaria, jaundice, renal failure, pregnancy related complications death (Adult)	PCR Confirmed	PMID: 15705338
49	Makkar et al – 2002	1	Thrombocytopenia (Adult)	-	PMID: 12495609
50	Patial et al – 1998 from Shimla	1	Cerebral dysfunction (Adult)	-	PMID: 9770881
51	Kakar et al – 1999 from New Delhi	1	Thrombocytopenia (Adult)	-	PMID: 10626136
52	Mishra et al – 1989 from Raipur	1	Cerebral malaria (Adult)	-	PMID: 2687230
53	Sachdev et al – 1985 from New Delhi	1	Cerebral Malaria (Child)	-	PMID: 3900435
54	Verma et al – 1976 from Jammu	1	Cerebral malaria (Child)	-	PMID: 776824

Medical History

Oaths of Doctors

Rudrajit Paul

All doctors are required to take an oath at the end of medical training. This is a form of unwritten contract between the doctor and the society. The concept of this oath can be dated back to the time of Hippocrates in Greece. But the practice is in vogue even today and this oath is a proud moment in a doctor's life. But there are numerous variations of this oath and it is constantly changing with changing morality and social dynamics.

The history of the oath starts with Hippocrates. But did Hippocrates himself actually pen it down? Scholars debate extensively over the origins of the first medical code of ethics (the oath). It was written probably between fourth and fifth centuries B.C.E. and probably after the death of Hippocrates. Was it the only oath at that time? Again, a question which is impossible to answer. But what is known for sure is the fact that after it was first published, this oath was lost to the scholars for more than a millennium, even in Greece. Then, in 1508, medieval German scholars started using this oath again in the University of Wittenberg. But only when the oath was translated into English two centuries later, that it became widely known and many western medical schools started using it. However, the mention of pagan Greek gods in the first line of this oath may have delayed its acceptance by Christian scholars in Europe. However, although Hippocrates' oath may be forgotten, his works were not. They were translated numerous times and formed the basis of medical education in Europe. Thus, medical scholars often read the text of the oath but they did not adopt it in a ceremonial manner. Medieval documents like Vaticanus Urbinates, Marcianus Venetus and Vaticanus Graecus have full text of the oath. These texts were used not only in Europe but also in the Jewish and Arab worlds. After Wittenberg, probably the University of Jena was the second one to adopt this oath as a ceremony. Later, European schools started reading the oath in Latin.

Were there other medical codes of ethics in the world? Definitely. Wherever medical science developed, the need for a code of ethics was felt. In India, the famed physician Charaka formulated his own code for physicians (described later). In 6th century C.E., the code of Asaph was written in the Hebrew medical texts. This code follows the spirit of the Hippocrates oath. In the Islamic world, the Hippocratic code was modified to reflect Islamic ideals.

In the Eastern world, Sun Szu-Miao developed a code in 7th century C.E. in China. It is translated as: **On the Absolute Sincerity of Great Physicians.** In Japan also, there was a code: **Seventeen rules of Enjuin.** Thus, all civilizations had independently developed a structure of the medical code of ethics.

It must be remembered that the original Hippocratic Oath is often slightly modified in translation through the ages. If a reader visits different websites for text of this oath, he/she will find slightly nuanced wordings, based on the language skills of the translator. However, the basic principles remain the same. Here, one accepted version of this oath is quoted.

Original Hippocratic Oath (Figure 1):

Figure 1: 12th century Greek manuscript of the Hippocratic Oath (the shape of the writing in form of a cross reflects Christian influence)

- I swear by Apollo Physician, by Asclepius, by Hygieia, by Panacea, and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture.
- To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else.
- I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong-doing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course. Similarly I will not give to a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art. I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as are craftsmen therein.
- Into whatsoever houses I enter, I will enter to help the sick, and I will abstain from all intentional wrong-doing and harm, especially from abusing the bodies of man or woman, bond or free. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets.
- Now if I carry out this oath, and break it not, may I gain for ever reputation among all men for my life and for my art; but if I break it and forswear myself, may the opposite befall me.

Limitations : -

1. Firstly, this oath is taken in the name of Greek gods. But this will not be acceptable to other religions now.

2. This oath forbids abortion. But abortion is legal and acceptable in modern society. Did Hippocrates actually forbid abortion? Or was it a later Christian addition during translations? This is a contentious issue because the medical texts written by Hippocrates contain detailed descriptions of abortion with no mention of the moral aspects.

3. In those times, surgeons were considered separate from physicians. This oath was then meant only for physicians. Hence, they are asked not to touch the knife. But now, all doctors are required to take this oath. So, this part will not be acceptable.

As limitations of this ancient oath became evident, the need for a new document, reflecting modern thinking was felt. In 1964, Louis Lasagna, the dean At Tufts University of USA (Figure 2) wrote a modern version of the medical oath. This is quoted below:

Modern Oath :

I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.

I will apply, for the benefit of the sick, all measures that are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.

I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.

I will prevent disease whenever I can, for prevention is preferable to cure.

I will protect the environment which sustains us, in the knowledge that the continuing health of ourselves and our societies is dependent on a healthy planet.

I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

Figure 2: The Tufts Medical Centre of Boston where the modern medical ethical code was written

Mainmonides was a famous Jewish Torah scholar and physician of the Middle ages(Figure 3). He wrote extensively on different legal matters, including the medical code. This is quoted below:

Figure 3: Maimonides Portrait from 1744

Oath of Maimonides:

The eternal providence has appointed me to watch over the life and health of Thy creatures. May the love for my art actuate me at all times; may neither avarice nor miserliness, nor thirst for glory or for a great reputation engage my mind; for the enemies of truth and philanthropy could easily deceive me and make me forgetful of my lofty aim of doing good to Thy children.

May I never see in the patient anything but a fellow creature in pain.

Grant me the strength, time and opportunity always to correct what I have acquired, always to extend its domain; for knowledge is immense and the spirit of man can extend indefinitely to enrich itself daily with new requirements. Today he can discover his errors of yesterday and tomorrow he can obtain a new light on what he thinks himself sure of today.

Oh, God, Thou has appointed me to watch over the life and death of Thy creatures; here am I ready for my vocation and now I turn unto my calling.

As is clear from the text, this oath is heavily influenced by religion and is the prayer of the physician to God. Some medical schools still use this text.

However, after the Second World War, the need for a secular humanistic medical code was felt. This was especially true after the atrocities by Nazi doctors in concentration camps. Thus, the world medical association started making secular codes which can be adopted everywhere. This document is modified periodically to reflect the changes in human thinking and political paradigm shifts. This oath is the most popular one used all over the world and the author of this article also remembers reading this oath at the end of medical training.

Geneva declaration :

1949 : The first one

I SOLEMNLY PLEDGE myself to consecratemy life to the service of humanity.

I WILL GIVE to my teachers the respect and gratitude which is their due;

I WILL PRACTICE my profession with conscience and dignity;

THE HEALTH OF HY PATIENT will be myfirst consideration;

I WILL RESPECT the secrets which are confided in me;

I WILL MAINTAIN by all the means in my power, the

honor and the noble traditions of the medical profession;
MY COLLEAGUES will be my brothers;
I WILL NOT PERMIT considerations ofreligion, nationality, race, partypolitics or social standing to intervene between my duty and my patient;
I WILL MAINTAIN the utmost respect for human life from the time of conception; even under threat, I will notuse my medical knowledge contrary tothe laws of humanity.
I MAKE THESE PROMISSES solemnly, freely and upon my honor.

2006: the Most modern one

I SOLEMNLY PLEDGE to consecrate my life to the service of humanity;
I WILL GIVE to my teachers the respect and gratitude that is their due;
I WILL PRACTISE my profession with conscience and dignity;
THE HEALTH OF MY PATIENT will be my first consideration;
I WILL RESPECT the secrets that are confided in me, even after the patient has died;
I WILL MAINTAIN by all the means in my power, the honour and the noble traditions of the medical profession;
MY COLLEAGUES will be my sisters and brothers;
I WILL NOT PERMIT considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;
I WILL MAINTAIN the utmost respect for human life;
I WILL NOT USE my medical knowledge to violate human rights and civil liberties, even under threat;
I MAKE THESE PROMISES solemnly, freely and upon my honour.

In 2017, further points were added to this list of codes:

- I WILL RESPECT the autonomy and dignity of my patient.
- I WILL SHARE my medical knowledge for the benefit of the patient and the advancement of healthcare.
- I WILL ATTEND TO my own health, well-being, and abilities in order to provide care of the highest standard.

Thus, as these serial changes make clear, the code of ethics is rapidly changing to reflect the complex realities of medical life. For example, health of doctors is now considered an important aspect of the profession. Similarly, civil liberties and autonomy of the patient is also considered vital now.

Recently, in some parts of India, some medical schools have started the “CharakShapath”. This is administered in Hindi, one of the 22 constitutional languages of India. The text is given below :

Charakshapath : (translated from archaic Sanskrit)

- तूब्रह्मचारीकाजीवनबितायेगाअपने बाल और दाढ़ी बढ़ाएगाकेवलसत्यभाषण ही करेगा। माँस नहीं खाएगाआहार में केवल शुद्ध वस्तुएँ ही लेगाईर्ष्या से मुक्त रहेगा तथा कोई हथियार धारण नहीं करेगा। राजा के प्रति घृणा अथवा किसी अन्य की मृत्यु अथवा कोई भी अधार्मिक कृत्य अथवा विनाश उत्पन्न करने वाले कृत्यों को छोड़ तू सभी अन्य कार्य मेरे आदेश पर ही करेगा।
- तू स्वयं को मेरे प्रति समर्पित कर देगा तथा मुझे अपना स्वामी समझेगा। तू मेरे अधीन रहेगा तथा सदा मेरे कल्याण एवं प्रसन्नता के लिए आचरण करेगा। तू एक पुत्र अथवा दास अथवा आश्रित के रूप में मेरी सेवा करेगा तथा मेरे साथ रहेगा। तू अहंकार-रहित होकर सावधानी और ध्यान से तथा एकाग्रह मनविनयस्थायी चिंतन एवं उन्मुक्त आज्ञाकारिता के साथ व्यवहार एवं कार्य करेगा। मेरे आदेश पर या अन्यथा कोई कार्य करते हुए तू अपनी श्रेष्ठतम योग्यताओं के साथ अपने गुरु के हितों की उपलब्धि हेतु ही आचरण करेगा।
- यदि तू धरती पर चिकित्सक के रूप में तथा मृत्यु के पश्चात स्वर्ग में सफलता एवं ख्याति प्राप्त करने का इच्छुक है तो तुझे गऊएवंब्राह्मणसे लेकर सभी प्राणियों के कल्याण हेतु प्रार्थना करनी होगी।
- तू दिन-रातभले ही कार्य में व्यस्त रहेतू अपने जीवन अथवा अपनी रोज़ी की परवाह किये बिना रोगियों को राहत पहुँचाने का हर संभव प्रयास करेगा। तू विचारों में भी परगमननहीं करेगा। तू दूसरों की वस्तुओं की ओर आँख उठाकर भी नहीं देखेगा। तू अपनी वेषभूषा एवं जीवन सादा रखेगा। तूशराबका सेवन नहीं करेगापापनहीं करेगा और न ही किसी प्रकार पापी की सहायता करेगा।

- तू सदा नम्र, शुद्ध, धार्मिक, प्रीतिकर, समुचित, सच्चे, हितकर तथा मृदु वचन बोलेगा। तेरा व्रताव समय एवं स्थान की दृष्टि से उपयुक्त तथा गत अनुभवों से सतर्कतापूर्ण होगा। तू सदा ज्ञान-प्राप्ति के ध्येय हेतु ही कार्य करेगा।
- तू उन व्यक्तियों का इलाज नहीं करेगा जो राजा से घृणा करते हों अथवा जिनसे राजा तथा प्रजा घृणा करती हो। इसी प्रकार तू उनका भी इलाज नहीं करेगा जिनका चरित्र एवं आचरण अस्वाभाविक, दुष्टतापूर्ण एवं दुःखद हो, जिन्होंने अपने सम्मान को न्यायसंगत न ठहराया हो तथा जो मृत्यु-बिन्दु पर पहुँच चुके हों तथा उस स्त्री का भी उपचार नहीं करेगा जिसकी सेवा-शुश्रूषा करने के लिए उसका पति अथवा कोई संरक्षक मौजूद न हो।
- पति अथवा संरक्षक की आज्ञा बिना किसी स्त्री द्वारा दी गई भेंट को भी तू स्वीकार नहीं करेगा। किसी भी रोगी के घर में तू किसी ऐसे व्यक्ति के साथ ही प्रवेश करेगा जो रोगी का परिचित हो अथवा उसने रोगी की आज्ञा ले रखी हो। तू अपने शरीर को भली-भाँति ढके रहेगा, धीर की भांति सिर झुकाए रहेगा तथा बार-बार विचार करके ही आचरण करेगा। गृह में प्रवेश करने के पश्चात तेरी वाणी, मस्तिष्क, बुद्धि तथा ज्ञानेन्द्रियाँ पूर्ण रूप से केवल रोगी की सहायता के तथा उसी से सम्बन्धित बातों के अतिरिक्त किसी अन्य विचार में रत नहीं होंगी।
- रोगी के गृह के विशिष्ट रीतिरिवाजों के बारे में तू अन्य किसी को भी कुछ नहीं बताएगा। यह जानते हुए भी कि रोगी की जीवनलीला समाप्त होने वाली है, तू इस बात को वहाँ किसी से भी नहीं कहेगा अन्यथा रोगी या अन्य व्यक्तियों को धक्का लगेगा। "भले ही तू कितना ही ज्ञान प्राप्त कर चुका हो, तुझे अपने ज्ञान की बड़ाई नहीं करनी होगी। अधिकांश व्यक्ति उन व्यक्तियों के शेखी बघारने से चिढ़ उठते हैं जो अन्यथा भले एवं विशेषज्ञ होते हैं।

Problems with this Indian oath :

1. This oath reflects the feudal past of India. In many areas of this oath, allegiance to the king is stressed repeatedly.

2. The oath reflects a certain puritan mentality. Doctors (obviously male) are expected to be celibate and vegetarian!!

3. This oath stresses on the need to remain under the teacher throughout life. But this mentality is not acceptable in modern society. Now, after passing out of college, the young doctors are expected to fend for themselves. Hence, allegiance to the teacher is not important now. Many people will emigrate for better salary to other places. There, they have to be on their own.

4. It is said that doctors should perform no sin. But what is sin? The definition of sin changes with time. For example, 500 years ago, touching a lower caste person was a sin for a Brahmin. But is it so now?

5. This oath forbids accepting gift from female patients. But this mentality is outdated now.

6. It is said that the doctor should not treat anyone who is against the king. But this is a fundamental violation of human rights. Doctors have to treat anyone in need.

So, there are various oaths and different parts of the world use different versions. When a young doctor reads the oath at the end of medical school, often the version is determined by the school authority and the youngster is not in a position to choose a particular oath. But later in life, he/she may find another oath more appropriate. What is important is to imbibe the basic good qualities (avoiding limitations) of all versions. For example, the American modification of the Hippocratic oath (Lasagna) has a very good point: don't be afraid to say "I do not know".

Also, many of the oaths end with the wishful thinking that if doctors follow the tenets, they may enjoy a fruitful life and reputation. But this wish mostly does not come true. Even if a doctor does everything according to moral standards, now he/she can be trapped in a consumer case and this may destroy his/her social position completely. That is why the modern Geneva declarations do not have this utopian point about social prestige or a good life any more.

Common misconceptions :

In the popular media, there are many misconceptions about medical oath

1. The oath taking is often glorified in movies and TV dramas. But the sense of duty to humanity develops inside a doctor throughout the six years of medical

training. Not at one moment of oath taking.

2. The oath is thus more important as a ceremony than an actual guide to doctors

3. The oath is not concerned with the business aspect of medicine. Like any other profession on this planet, medical profession is also a business (guided by consumer laws) where the doctor can expect fair remuneration for his/her services. These charges are determined by the market like other essential commodities (food, electricity etc.) Some people in Indian media often cite this oath as a proof of selfless and free service of doctors. Doctors do a lot of selfless service anyway without the need for invoking the oath. But the oath does not direct them to work for free. (this is the fundamental problem of physicians now: by Indian law the medical field is a business {since it is governed by consumer laws}, but by their training, it is supposed to be a selfless service)

4. After the 2017 Geneva declaration, a doctor has full right to take care of his own health. Thus, service to humanity must be balanced with self-care. A doctor should not jeopardize his/her own health for undue reasons.

5. A doctor should not expect in modern society that just because he/she has taken the oath, the society will give him/her a good life or reputation. The doctor has taken the oath to serve the society. The society has not taken any oath to reciprocate!!!!

There are many medical schools in the world that does not administer any oath at the end of medical training. Does it matter? Certainly not. What is important is the fact that modern doctors should act according to their inner conscience and available evidence. The medical code does not demand anything superhuman from doctors. It just states that doctors should be human.

Drug Corner

Cardiovascular Outcome Trials in Indian Perspective : A Call to Indian Drug Regulators

Shambo Samrat Samajdar[1], Shatavisa Mukherjee[2], Shashank Joshi[3], Santanu Kumar Tripathi[4]

India's gradual approach in being the Diabetes Capital of the World, has vulnerably exposed its diabetic population to multiple anti-diabetic drugs. At this very outset, it is important to adjudge the cardiovascular safety of these anti-diabetic medications, evidenced by good quality RCTs.Though US FDA has recommended to evaluate cardiovascular safety of anti-diabetes agents during their development process, there are still a few such drugs which is present in Indian pharmaceutical market without any cardiovascular outcome data. Thus, any antidiabetic drug being permitted for marketing in India should undergo cardiovascular outcome trial (CVOT) and Indian drug regulators should be much vigilant in this regard. The present review tried outlining some basics of CVOTs, with special reference to its conduct in Indian population.

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Key words **: Cardiovascular Outcome Trials, Indian Drug Regulators, Anti-diabetic Medications, US FDA.**

Statistics suggest that 2 out of 3 deaths in diabetes are due to cardiovascular (CV) disease. Management of diabetes should be a holistic approach, which should not only focus on HbA1c lowering but also take CV risk into its account. To monitor cardiovascular outcomes while prescribing antidiabetic drug is of utmost importance. After the 'rosiglitazone saga' in 2007 where FDA revealed its own meta-analysis of CV events with rosiglitazone which showed a statistically significant increase in risk (RR = 1.4). In October 2007, FDA had issued a 'black box warning' of ischaemic events for rosiglitazone and finally on December 2008 drug manufacturers were directed for the requirement of CV outcomes trials (CVOTs) for anti diabetes medications. The year 2008 acts as a watershed line prior which prime focus of diabetes management was targeting glycaemia, post 2008 diabetes management also emphasizedextra-glycemic targets like CV protection and CV safety concerns.

FDA's guidance on CVOT :

As per 2008 FDA guidance, adequate evaluation of CV safety is warranted in development of type 2 diabetes drug developments. It is required that the phase 2 and 3 trials of this kind should include patients with high risk of CV events(CV mortality, MI, stroke,hospitalization for ACS, urgent revascularization procedures, HF hospitalization), with trials having adequate sample size and considerable duration to detect CV events thus allowing a meaningful evaluation of CV risk. Independent adjudication of CV events followed by meta-analysis of the phase 2 and 3 trials to be conducted at the end of the research program. Substantial premarketing data analysis comparing the CV events due to candidate drug vis-à-vis control group is mandated. An upper limit of a two-sided 95% CI of the estimated risk ratio is less than1.8 should be accomplished in a separate, large CV safety trial, if the same cannot be done through meta-analysis. For agents whose upper limit of 95% CI falls between 1.3 and 1.8 in premarketing analysis, completion of a post-

Editor's Comment :

- Diabetes patients have higher risk to develop cardiovascular diseases
- US FDA recommended to evaluate cardiovascular safety of anti-diabetes agents during their development process
- Indian population are more vulnerable to cardiovascular diseases compared to western population
- There are a few anti diabetes drugs which is present in Indian pharmaceutical market without any cardiovascular outcome data
- Indian drug regulators need to be more vigilant regarding such dugs
- Considering the cost of CVOTs industry may consider different adaptive design to reduce time and expenditure.

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marketing trial or continuation of a premarketing trial after approval may be needed. Insulin was specifically excluded from its CV safety evaluation in the FDA's guidance.

Why India is so important in this regard ?

In India, more than 10.5 million deaths occur annually, and it was reported that CVD led to 20.3% of these deaths in men and 16.9% of all deaths in women. Prevalence data of cardiovascular diseases in South Asian population is suggestive of a dreadful condition. Studies conducted on South Asians in western countries have revealed earlier onset, higher incidence, and higher standardized mortality rates from ASCVD in South Asians compared with others. The major biological mechanisms contributing to this excess risk are their alteredmetabolic profile including elevated plasma insulin levels, altered plasma lipid profile, and higher truncal skin-fold thickness. South Asians exhibit at least two times increased T2DM prevalence, a higher incidence of new-onset diabetes mellitus, and a higher prevalence of impaired glucose tolerance. Studies comparing South Asian individuals residing in India with those residing in the United States reveals that South Asians in the United States have higher plasma levels of triglycerides, total cholesterol, and LDL-C and lower levels of HDL-C, which can be probably attributed to higher prevalence of insulin resistance in this populationand abnormalities in CETP. The MASALA study and others have demonstrated that South Asians and Asian Indians have a high prevalence of CAD despite a lower prevalence of some traditional risk factors for CAD. Moreover, Asian, Americans are also shown to be at a higher risk for renal disease and renal failure compared with NHWs, and diabetes mellitus and high blood pressure appear to be contributing factors, among others. Amongst various nonbiological mechanisms, lower physical activity rate, use of tobacco products adds to increased risk of ASCVD in south Asians. Moreover, diets here are rich in carbohydrate, saturated fats and low fruits and vegetables.

Median scores for South Asians was higher in QRISK2 algorithm which has been derived and validated to accurately estimate CVD risk and detect subclinical CVD in different ethnic groups in England and Wales and takes into account South Asian ethnicity as an additional risk factor.

CT has been able to demonstrate the following :

South Asians display more severe CAD on CT as determined by both increased mean percent stenosis and a higher number of patients with multiple diseased vessel segments. 47 Asian Indian race is a significant independent predictor of CAC severity, even when controlling for traditional risk factors for CHD. The prevalence of high CAC burden (scores >100) among Asian Indians is greater than in all other ethnic groups (NHWs, Asians, Hispanics, and blacks among those >60 years of age). A longer duration of residence in the United States has been associated with higher levels of CAC in South Asians in the MASALA study.

Antidiabetic Drugs in India and CVOT :

With India's gradual approach in being the Diabetes Capital of the World and Indians being more vulnerable to develop cardiovascular diseases, we are vulnerably exposed to multiple anti-diabetes drugs. Antidiabetic drugs thus being permitted for marketing in India also should undergo CVOT and Indian drug regulators need to be more vigilant on this regard. It is extremely important to prescribe anti diabetes drugs with proven CV safety profile. Though full result of CAROLINA is still awaited, of available new anti-diabetic drugs in India,sitagliptin and linagliptin are cardio safe. Empagliflogin, canagliflogin, dapagliflogin show benefits in CVOTs. Liraglutide and dulaglutide also show benefits in their respective CVOTs. Lixisenatide is CV safe as per their CVOT.

Teneligliptin, evogliptin and remogliflozin are marketed in India without any cardiovascular outcome

Class	Trial	Intervention	Primary Outcome	Secondary Outcome	CV Death
DPP-4 inhibitors	SAVOR-TIMI EXAMINE TECOS	Saxagliptin Alogliptin Sitagliptin	3-point MACE1.00 (0.89–1.12) 3-point MACE0.96 (95% UL≤1.16) 4-point MACE0.98 (0.89–1.08)	Expanded MACE 1.02 (0.94-1.11) 4-point MACE0.95 (95% UL ≤1.14) 3-point MACE0.99 (0.89–1.10)	1.03 (0.87–1.22) 0.85 (0.66–1.10) 1.03 (0.89–1.19)
SGLT2 inhibitors	EMPA-REG CANVAS	Empagliflozin Canagliflozin	3-point MACE0.86 (0.74–0.99) 3-point MACE0.86 (0.75–0.97)	4-point MACE0.89 (0.78–1.01)	0.62 (0.49–0.77) 0.96 (0.77–1.18
GLP-1 receptor agonists	ELIXA LEADER SUSTAIN-6 EXSCEL	Lixisenatide Liraglutide Semaglutide Exenatide	4-point MACE1.02 (0.89–1.17) 3-point MACE0.87 (0.78–0.97) 3-point MACE0.74 (0.58–0.95) 3-point MACE0.91 (0.83–1.00	Expanded MACE 1.00 (0.90–1.11) Expanded MACE 0.88 (0.81–0.96) Expanded MACE 0.74 (0.62–0.89)	0.98 (0.78–1.22) 0.78 (0.66–0.93) 0.98 (0.65–1.48) 0.88 (0.76–1.02)

trials. It signifies the inappropriateness of using these drugs in diabetics associated with cardiovascular diseases. Though opposed school of thought impresses upon the huge cost of therapy due to these CVOTs, designs like factorial design and adaptive design may reduce the time and expenditure for doing CVOTs. CVOTs can be performed along with phase 2 and 3 trials and data may be obtained suggesting the safety of the candidate drug.

Appeal to Regulators :

Each diabetic patient possesses the right to access a cardio safe antidiabetic medication, evidenced by good quality RCTs. It thus remains a responsibility of Indian regulators to respect such rights and be much more vigilant in allowance of these drugs in Indian market only with robust CV safety data.

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Knowledge Update

Prone ventilation : The essential facts

Rudrajit Paul, Jyotirmoy Pal

In the era of Covid-19, mechanical ventilation has become the buzzword of the medical community. Also, among the various modalities of mechanical ventilation, prone ventilation has become a popular treatment method. At this juncture, it may be necessary for every physician to have a basic knowledge of this ventilator technique. This short article will try to highlight the essential characteristics of prone ventilation.

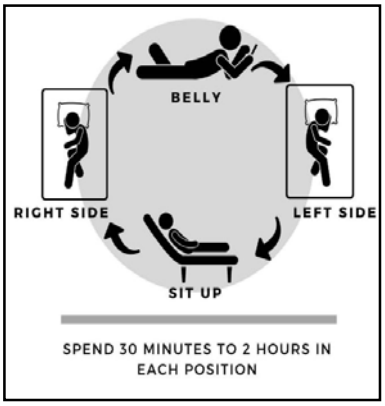
Indications :

- Severe ARDS, when there is refractory hypoxia
- Wounds or burns in the back which make supine position impossible

But there are certain **contra-indications** to prone positioning:

- Extreme obesity
- Ascites
- Hemodynamic instability etc..

So, the basic premise of prone ventilation is that the patient will be put in prone position for long hours (typically 12-16 hours per day) while on mechanical ventilation. This daily change of position requires a highly trained team of staff (at least 3-4, working in unison). The patient in prone position must have eye protection, pressure ulcer care and airway care.



Usually these patients are on continuous deep sedation with or without neuromuscular blockade.

Physiology of prone positioning :

In supine position, the weight of the mediastinal structures and also some upper abdominal viscera increases the dorsal pleural pressure (for example, the heart contributes approx. 3-5 cm of water pressure on the dorsal lungs). This reduces the transpulmonary pressure (the pressure which is responsible for alveolar ventilation) in the dorsal areas of the lung and increases the chances for atelectasis. In normal persons, this is of minimal significance. But in ARDS, when the lung is already edematous, this physiology severely compromises ventilation in dependent dorsal lung regions. Placing the patient in prone position reduces the pleural pressure and helps improve alveolar air-flow. It has been observed that there is significant improvement in oxygenation after prone positioning in ARDS.

The second advantage of prone ventilation is prevention of ventilator induced lung injury (VILI). Prone position makes lung density, alveolar ventilation and transpulmonary pressure homogeneous throughout the lungs. This reduces the chances of atelectrauma. Alveolar recruitment is increased and hyperinflation or volutrauma is reduced.

Prone positioning also allows better pulmonary secretion drainage and change in mechanics of the chest wall allows the lungs to inflate at lower pressures.

Trials :

The PROSEVA trial (2013) (published in NEJM) was the first to show clear benefit of prone ventilation in ARDS. It showed that there was a clear mortality benefit up to 90 days after prone positioning. But prone ventilation in isolation does not benefit the patient. It must be used in conjunction with other ventilator strategies like low tidal volume, high PEEP or the use of pressure controlled mode.

Complications:

1. Reduced enteral feeding
2. Displacement of airway tubes
3. Facial edema
4. Difficulty in performing procedures like catheter insertion etc.....

Self-proning/auto-proning :

This method has become popular after the covid-19 pandemic. In covid-19 infections with hypoxia, many western hospitals have initiated the technique of making the awake patients lie in prone position early in the hospital course. This is done improve oxygenation and delay the need for mechanical ventilation. A small observational study has shown that self proning can improve oxygen saturation quickly but whether this will really help in long term management is still a matter of debate.

Conclusion :

Prone positioning is a good method of treatment of severe ARDS, especially in acutely developing ARDS like Covid-19 infection. But this is a highly labour intensive procedure and requires dedicated healthcare staff round the clock. This may not be feasible in most hospitals of India.

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Mediquiz

Series - 6

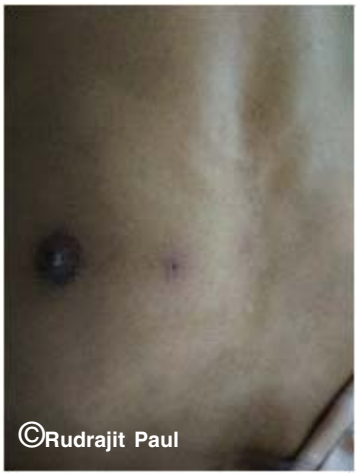
Rudrajit Paul
Quiz Master

Fever with rash

1. A 12 year old boy was admitted with fever, headache and seizures. Later, on examination, a fine morbilliform rash was found on his trunk. Which of the following is the LEAST likely cause of his presentation ?

a. Japanese encephalitis
b. Scrub typhus
c. Dengue fever
d. SLE

2. A 32 year old man presented with high fever and unconsciousness. On examination, a macular rash was found on the trunk. Also, the following clinical finding was noted. Which is the drug of choice in this case?



a. Azithromycin
b. Doxycycline
c. Ceftazidime
d. Caspofungin

3. A six year old girl presented with high fever, erythematous rash and sore mouth. On examination, large lymph nodes were found in the neck. One night, she suddenly complained of severe chest pain. What is the most probable diagnosis?

a. Rheumatic fever
b. Kawasaki disease
c. Infectious mononucleosis
d. Bubonic plague

4. Which of the following skin rashes have been reported in Covid-19 infection?

a. Exanthema
b. Urticariform
c. Varicelliform
d. All of the above

5. A 49 year old male patient presented with fever for three weeks and chest pain. He is known to use injectable heroin sometimes. On examination, the following rash is found:

Which Criteria is useful for diagnosis of this patient?

a. Jones criteria
b. Ghent criteria
c. Duke criteria
d. Hunter criteria

6. A 12 year old girl presented with fever and a rash. The rash was erythematous, macular and mainly found on palms and soles. In addition, there is body ache and malaise. Which of the following is the LEAST likely cause of this presentation?

a. Erythema multiformae
b. Rat bite fever
c. Scrub typhus
d. endocarditis

(Answer : next page)

Answer : Mediquiz

Answers : -

1. A

Japanese encephalitis virus infection does not have a rash. All the other causes of encephalitis mentioned here may present with rash. Dengue has now emerged as an important cause of encephalopathy during epidemics. The rash in dengue infection is biphasic. At first, there is an erythematous confluent rash; later purpura may appear.

2. B

This clinical image shows an eschar. Based on the history, this is probably a case of scrub typhus. So, doxycycline is the drug of choice. Azithromycin is also used in scrub typhus but since this case has encephalopathy, doxycycline will be preferable.

3. B

Kawasaki disease is common in children< 8 years of age. The most dreaded complication of this disease is coronary arteritis, leading to myocardial infarction or aneurysm.

4. D

All these types of skin rashes have been reported in Covid-19 infection till now. Cutaneous manifestations have been found to be an important clinical feature of Covid infection. Sometimes, these rashes may be confused with other infectious diseases.

5. C

Duke's criteria is used to diagnose infective endocarditis. This injectable drug using person has prolonged fever and the rash in hands is suggestive of Osler's nodes. So, this is likely to be a case of infective endocarditis. Ghent criteria is used to diagnose Marfan syndrome. Hunter criteria is used to diagnose Serotonin toxicity.

6. C

The rash in this case is mainly distributed in the extremities. Among the given options, scrub typhus has predominantly a truncal rash. All other diseases mentioned here have peripheral rash.

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

ECG : The Other Face (JIMA, Vol 118, No 6)

Sir, — TECG is one of the most incredible discovery in medicine, which is reflected from its usefulness in day to day clinical practice. Willem Einthoven receivedNobel Prize in physiology/medicine (1924) which is testimonial to its unique ability to diagnose and understand various cardiac disorders. Over Last one decade, ECG has been established as a very cost effective diagnostic and prognostic modality. Its role in various cardiac conditions such as STEMI can't be overemphasised. Its often helpful in non cardiac conditions also. In this paper, author has highlighted various such conditions. Pulmonary thromboembolism (PTE) is a potential life threatening situation which poses a significant diagnostic challenge. There are a gamut of ECG signs which are helpful in suspicion and diagnosis of PTE. Symmetrical T wave inversion in anterior chest leads (V1-V3) is common and reflects RV strain due to acute PTE. Other ECG signs such as S1Q3T3though nonspecific, should be considered under appropriate clinical settings. One must be aware of various non cardiac conditions such as SAH, GI disorders, electrolyte imbalance, poisonings which can mimic changes of coronary ischemia as nicely depicted in this paper. A wrong management in lines of coronary artery disease may be detrimental in these patients.

ECG is also subject to change under changing physiological conditions such as posture, pregnancy & skeletal abnormalities, which may be misinterpreted as abnormal. Undoubtedly ECG is an opportunity to detect various non cardiac conditions. No ECG sign should be considered "sine qua non"of any particularcondition, since ECG changes are subject to limitations of sensitivity & specificity. In depth knowledge and wise approach to ECG reading is a formidable tool of clinical practice.

Prof and Head of Cardiology, **Gurpreet Singh Wander**
DAV Medical College,
Ludhiana, Punjab - 141001

Untouchability – Other Face of Pandemic (JIMA, Vol118, No 6)

Sir, — I sincerely thank and laud the Editor Prof Jyotirmoy Pal for bringing up the issue of dilemma of doctors in the context of COVID-19 pandemic in India, in his timely Editorial "Untouchability – Other Face of Pandemic"; my only commiseration being that JIMA is read only by doctors and does not reach the public at large.

While I find the attitude of the common person in evicting a health care worker (not only a doctor, but also a nurse, an ambulance driver or, a even a scavenger) from his or her apartment repugnant, I tend to ascribe this to a sense of unfounded panic rather than an expression of genuine hate or, pent up anger against these people.

However, I find the carefree attitude of the same common person thronging streets (more concerning, cafes and other enclosed spaces of socializing) without following physical distancing, neither wearing mask (at best using one to

protect the chin!) unacceptable. An undeniable result is unabated spread of the virus with consequent morbidity and mortality; this closes the loop with more panic in society.

How do I see the way forward? What is my wish list for different strata of society?

Doctors (and other health care workers) should remain committed to their core job; this does not mean only serving COVID-19 patients; this involves providing usual service in all different specialties; myocardial infarction still needs thrombolysis, fractured neck femur requires hemiar throplasty, diabetic ketoacidosis demands insulin infusion and pregnancy looks forward to safe delivery. Fear of COVID-19 should not thwart any of these activities. It need not be stressed that health care workers need to follow strictest precautions (does not mean PPE in all situations) not only at place of work so they don't pick up the virus, but also once they return home so that they don't spread to near and dear ones. I would go as far as to state that infection in a health care worker should be looked upon as a failure to follow preventive measures; this, in no way, diminishes my appreciation and respect for so many of my brothers and sisters who have been affected and have even laid down their lives. With treatment paradigm changing quickly, it is our onus to keep abreast of the latest. Each patient, especially the more severely affected, and the family deserve our unstinted empathy and support. We should also try and impress on everyone around us, patient or, passerby, the importance of self-protection.

Government and employers of health care workers need to facilitate the process by every possible support, from helping in comfortable transportation, providing a safe work environment, making protective equipment freely available, arranging for state-of-the-art treatment facility, to preventing burn-out from overwork and stress and assuring prompt and quality medical care (even in private hospital) if anyone is affected; finally, there must be assurance of very generous compensation in the unfortunate event of demise of a health care worker from COVID-19.

Media have an extremely important role of sensitive reporting, not looking at distress as opportunity for a 'headline story'. I would like them to further consolidate efforts to educate and counsel the common person to ameliorate uncalled for panic and resultant irrational behavior. They should continue to disseminate public health measures like physical distancing, wearing of proper face cover, hand washing/ sanitizing and the rest. They need to be more pro-active in speaking out against the unfair treatment meted out to health-care and various other essential service providers (like police, transport workers, power plant workers, supply chain workers and so on).

Common person needs to be extremely vigilant in following preventive advice, avoid groundless fear, appreciate difficulties faced by health care personnel and not act irrationally on impulse.

I acknowledge containing this pandemic is still a huge struggle. But we can justifiably take hope from success stories of a number of countries by strict enforcement of public health measures, likely availability of more effective treatment (as we understand the course of disease better) and eventually preventive vaccine that will,hopefully, be affordable and available to whoever needs it.

Prof and Head, Department of Endocrinology, IPGME&R, Kolkata **Subhankar Chowdhury**

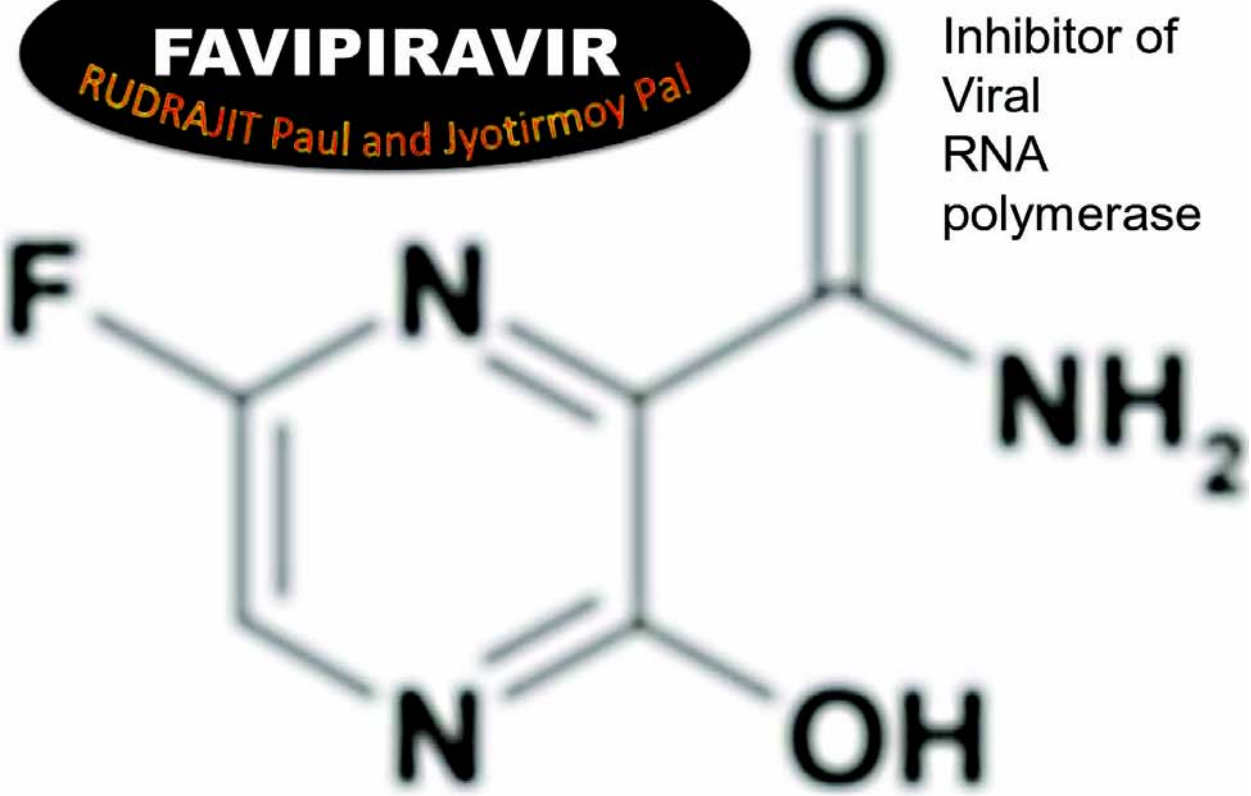
Access to Medicines Licensed for Management of Covid-19 in India

Sir, — On July 11, 2020, there is yet another addition to the Covid-19 pharmacotherapy armamentarium in India (welcome this!) after remdesivir, favipiravir and dexamethasone. Biocon-India receives 'restricted emergency use' marketing license from Drugs Control General of India for itolizumab, an anti IL-6 monoclonal antibody hitherto used for treating psoriasis, repurposed now for use in moderate to severe Covid-19 patients. But there is a serious concern about access of patients (of Covid-19) to these medicines that are not freely available in the open market. It is learnt that people (doctors and hospitals) all over India are struggling to access these drugs for treating Covid-19. This is just not acceptable. What's needed is local governments and hospitals should amend the usual policy and rules for procurement of drugs and health technologies for adequately addressing the legitimate need and demand of (and during) a pandemic like this (Covid-19), and bring to fore special strategies instead. Many such authorities (local governments and hospitals) seem to be either clueless or uninformed about how to proceed for procurement (and distribution to the point of care) of such medicines. Should not they be proactive in directly contacting the concerned companies for bulk procurement of these drugs - Hetero/Cipla for Remdesivir, Glenmark for Favipiravir, and now Biocon for Itolizumab? One should appreciate that at this stage, all these companies have only limited manufacturing capacity for these drugs that can hardly match the demand in the country. There is an obvious competition among different governments/hospitals for stockpiling these drugs. As a professional clinical pharmacologist as well as a concious citizen, I feel worried about this issue of lack of access to these essential medicines when you need them most. This is an unforeseen crisis and there are unique and special challenges. We must evolve unique and special solutions for them. Yours sincerely, .. Dr Santanu Tripathi, Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata".

Prof and Head, Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata700073 **Santanu Kumar Tripathi**

FAVIPIRAVIR

RUDRAJIT Paul and Jyotirmoy Pal



Inhibitor of Viral RNA polymerase

Favipiravir (pro-drug) → Favipiravir-RTP → Inhibits viral polymerase

Initially developed for Influenza
Also active against other RNA virus
Recently used for Covid-19

Side effects:
Hepatitis, neutropenia, Hyperuricemia

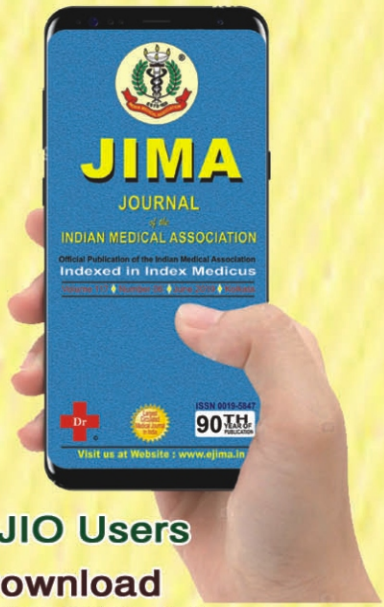
Dose for Covid-19:
Orally 1800 mg BD on day 1
Then 800 mg BD up to Day 14
Dose for influenza:
1600 mg BD on day 1
Then 600 mg BD for 4 days

Do not administer in pregnancy

Issued in Public interest by JIMA

Two Feathers in the Cap of Team JIMA in 2019

JIMA goes SMART



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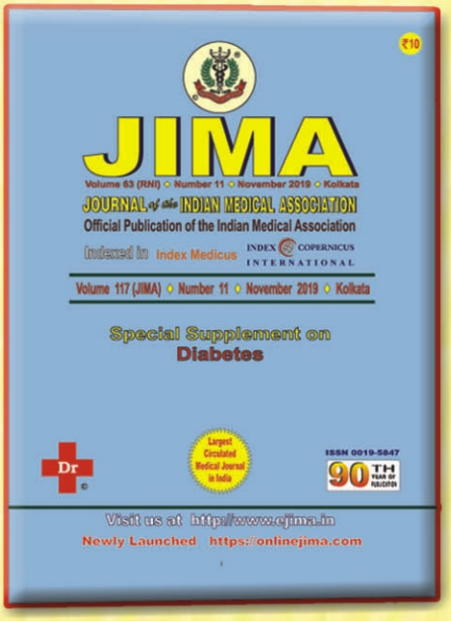

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