Rs.10

JIMA

Volume 64 (RNI) ◆ Number 09 ◆ SEPTEMBER 2020 ◆ KOLKATA

JOURNAL *Of the* INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in INDEX COPERNICUS INTERNATIONAL Index Medicus

Volume 118 (JIMA) ♦ Number 09 ♦ September 2020 ♦ KOLKATA

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Largest Circulated Medical Journal in India

ISSN 0019-5847

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JOURNAL OF THE INDIAN MEDICAL ASSOCIATION

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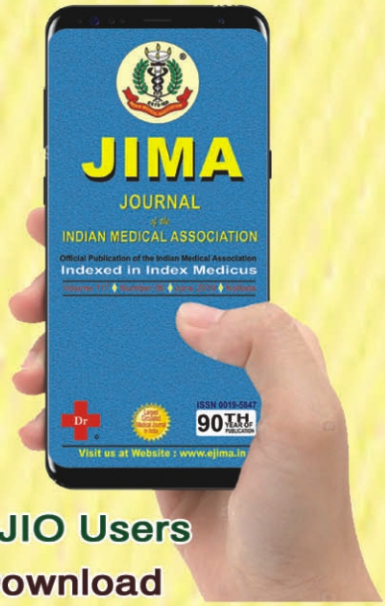

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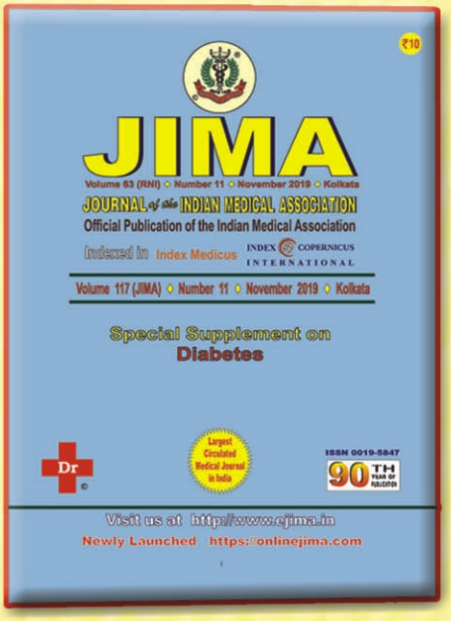

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Volume 118 (JIMA) ■ Number 09 ■ September 2020 ■ KOLKATA ISSN 0019-5847

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Editorial

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"It is health that is real wealth and not pieces of gold and silver."
— Mahatma Gandhi

"Health is a state of complete physical, mental and social well-being in which disease and infirmity are absent ."

"Public Health is Science and Art of preventing disease, prolonging life, and improving quality of life through organized effort and informed choices of society, organization, public and private communities and individual".
— World Health Organization

Health depends on a complex interplay among an array of genetic, environmental, and lifestyle factors. As a result, public health has become multidisciplinary and built on expertise and skills from many areas including biology, environmental science, sociology, psychology, statistics, and communication. This makes it difficult for the government and general public to understand. Public health is an intervention to prevent disease. After a heart disease, there are curative measures such as angioplasty or CABG; so, benefits are more obvious. But Public health measures do not provide direct benefits–as it helps in preventing diseases. So public health is not only difficult in implementation but also is less rewarding. That is a real challenge to a state.

Public health strategy has evolved from prehistoric period. It has undergone changes from decade to decade according to culture, education, economy, religion, and dynasty. While in the medieval period, the attitude of the rulers determined direction of public health; in twentieth century, it was decorated with democratic hues.

Prehistoric Ages in Civilization :

Ten thousand years ago, human beings were hunters. The only challenge was to find enough food. They moved into small groups and gradually the concept of 'Community' had developed. In early periods, It was thought that the occurrence of diseases was because of the curse of nature. Different myths, superstition prevailed and they considered worship of natural forces as remedies of disease. Gradually mankind learned the cultivation of crops and the use of domestic animals. Also, people stayed in groups. So mankind acquired diseases transmitted from animals and also from themselves. As a by-product of cultivation there was an accumulation of waste materials which were a good substrate for the growth of insects. Centuries passed with these beliefs.

Early Civilization :

Evidence of diseases found in early civilizations like Mesopotamia, Egypt and India. In Egyptian Mommy there were shreds of evidence of tuberculosis, Leprosy, Chickenpox. In Egyptian Literature Papyrus 3000 BC, the concept of the Public health system had developed, but still, people believed more on supernatural forces.

Ancient Civilization – India :

We observed the early Indian approach of Public health system in Harappa, Mohenjo-daro(3500-1500 BC). In excavation, there was evidence of a drainage system, particularly covered drainage, wells, and baths. Ayurveda, the Indian system of Medicine has given the importance of purity and cleanliness. Charaka described the aim of Medicine as–prevention of disease and Combating diseases. In the Post-vedic period, Ayurveda continued but was dominated by Buddhist and Jain teaching where surgery suffered a setback. From the inscription of Great Ashoka, it is evident that institutional approach (hospital)was adopted in Maurya Period. Medical Teaching got a boost in Gupta period.

Ancient Civilization – Greek Roman Period :

It is the thought of Greek physician Hippocrates, who instituted the concept that diseases were not due to the curse of God, rather a product of the activity of mankind–an imbalance between man and environment. Environmental factors, diet, personal behaviour were key issues behind occurrence of diseases. So he opened the concept of preventing diseases. Romans inherited the pathway of Greeks regarding sewage disposal,

sanitary baths and Galen (130-205 AD) taught the environment was the key issue in occurrence of diseases. They made notification of disease that can harm public health mandatory during this period.

Dark age in Europe and Medieval period in India :

With the fall of the Just in ianempire, the dark age of Europe started. The concept of Greek Physician was halted for centuries due to religious factors. No new knowledge was added. The dominance of the Church, superstition, and religious factors were key regulators of the health care system. On the other hand, there was growth in different civilisations with gradual overcrowding of cities. All human factors made soil for development of endemic and periodic epidemics. European society failed to halt the recurrent Plague epidemic. Black Death in the 14th century pushed a non confident sentiment against the religious pivotal system. People started adopting new measures to prevent the spread of the epidemic. Italy was a successful model in formulating measures against epidemics. Similar practices like Isolation, quarantine started even before the birth of Christ to prevent the spread of diseases, but it was in 1377AD when The Great Council of Ragusa(modern Croatia) enacted the law of isolation. Gradually, the whole of Europe adopted the method.

Effect of French Renaissance (15th to 17th Century) :

French renaissance brought fresh air in the human thought process. Black death was so devastating that the faith on the church as the saviour of mankind no longer existed. This brought a sudden end of the dark ages in Europe and the scientific thought process beyond the superstitious mind dominated. Andreas Vesalius dissected the human body and William Harvey described the circulatory system. Understanding of Medical sciences and diagnosis had improved and these thoughts were seedlings of the modern health care system.

Girolamo Fracastoro (1546) – Italian biologist was a pioneer if bringing the idea of Germ Theory before formally articulated by Louis Pasteur. In his book "***Decontagione et contagiosismorbis***", he speculated that each disease was caused by a rapidly multiplying seeds and was transmitted by air, direct contact, food, and water.

John Graunt (1662) – French Clerks began recording deaths. He analysed data and made extensive observations regarding common causes of death, seasonal variation, sex variation, population size, and growth rate. This was first articulated epidemiological research on population.

John Pringle and jail Fever (1740) – The Scottish Physician was a physician general in Austrian War (1740-48). In his book "***Observations on the diseases of the army***", he mentioned several measures like ventilation, sanitation, drainage, latrine can improve the health of soldiers. He also had written that hygiene can prevent typhus or jail fever which is common among war prisoners. He first coined the term "Influenzae".

James Lind and Scurvy (1754) – It was a common problem of Sailors because of the chronic lack of fresh vegetables and fruits during long sea voyages. Scottish naval surgeon suspected that citrus fruit can prevent this disease based on some anecdotal observations. He conducted the first clinical case-control trial of the world on 12 sailors with scurvy. Based on his recommendation Lemon juice was rationed to each sailor.

Industrial Revolution (eighteenth to nineteenth Century) :

The industrial revolution in eighteenth-century brought an explosion of development. At the same time, it brought explosion of problems in Europe. There was explosion of population and migration. Laborers used to stay in congested rooms, poor ventilation, trauma from machinery, toxic exposures brought new health problems in Europe. Moreover, Europeans started colonizing other continents for trading. So, the disease from one continent started to spread to other continents. It was the beginning of the Pandemic.

The Enlightenment (1700-1850) :

This was a period of democracy, citizenship, reasoning, rationality, and scientific thought. Jeremy Bentham provided the underpinning of health policies. It was a reduction of mortality and improvement of health policy that had an impact on the economy. Healthy people can contribute more in the economy of the state.

Ignaz Semmelweis (1840) :

He was a Hungarian physician in charge of the Maternity department of Vienna General Hospital. He observed Postpartum Sepsis (Fever) in increased frequency which was fatal. There were two maternity wards in the hospital. One was attended by midwives and the other was attended by medical students. It was observed that in the hospital attended by Medical students' infection rates were high and usually, students used to come immediately after doing dissection. After some period one of the colleagues of

Dr Semmelweis cut his hand during dissection and developed similar symptoms. Ignaz began to wonder whether contagion could be carried by hand and be transferred to women during childbirth. He proposed hand washing before performing delivery and this simple attempt dramatically reduced infection and death rate.

John Snow – Father of Epidemiology (1813-58) :

The cholera epidemic started in Jessore, now in Bangladesh. Cholera spread to England and became a major health issue in 1830. The prevailing concept was it was caused by miasmas and person to person contact. Thousands of people died due to several outbreaks of Cholera epidemic in England and America. Snow observed all patients came with gastrointestinal problems, not with respiratory symptoms. So he proposed possibly organism entered into the body by Fecal-oral route, not by inhalation. In 1949 he published the paper "On the Mode of Communication of Cholera" but did not get much attention of the medical community. Not being frustrated he continued to gather data on the pattern of disease and tried to get a link between water sources and the occurrence of cholera. From Municipal data, he observed in particular two areas where water was supplied by a Private company pumped from a particular well had the most occurrence of Cholera. In 1953, Cholera had broken in Broad Street in London. John Snow identified a local hand pump from where victims had taken water, whereas other residents who had not taken water were relatively safe. He appeared in front of the Municipal Board and urged to remove the hand Pump. In spite of the initial resistance Board finally removed and the outbreak subsided. Snow continued his investigation. He came to know the first victim of cholera was a child. His mother had emptied the pail of the infant's stool into a cesspool to seep in. That was the point of contamination.

Louis Pasteur (1822 - 1895) :

Though John Snow's investigation established transmission of disease, but what caused disease was not revealed until the discovery of the Germ Theory by Louis Pasteur. He was a French Biologist and Chemist. He studied the fermentation of wine, beer, and milk, and proposed microorganisms was responsible for the occurrence of diseases. Pasteur was a pioneer in generating the idea that weakened organisms can be used as a vaccine and he successfully generated a vaccine against rabies.

Florence Nightingle (1820- 1910) :

Nightingale had learned from Belgian statistician L.A.J Quetelet that different medical treatments had negligible effects on outcomes; also that institutions, like a foundling hospital, with the most benevolent of intentions—saving infant lives—nonetheless had high mortality rates. Her own experience in the Crimean War, carefully written up afterward in 'Notes on Matters Affecting the Health, Efficiency and Hospital Administration of the British Army, 1858', showed appalling mortality rates from disease, despite the provision of a system of hospitals. She attributed these terrible death rates to underlying sanitary conditions—soldiers weakened by months of poor food and cold, and then subjected to badly overcrowded conditions when in hospital. The mortality rates did not go down until a visiting team of sanitary experts had the sewer system cleaned out and other engineering work undertaken.

Caution about unintended results led to Nightingale's insistence that new social programs start small. Get some experience first, she advised: see how the institution (hospital, program, ward, training school, prison, whatever) works before you are committed to large buildings, fixed programs, etc. Nightingale became a pioneer advocate of what would later be called "**evidence-based health care**," and did some of the pioneering work in data collection with "**uniform classification of disease**" so that comparisons in outcomes could be made.

Sanitary Idea (1850-75) :

In 1942 Sir Edwin Chadwick a social reformer published a report that life expectancy was much lower in urban areas than the countryside. He also pointed out that improper drainage system, polluted drinking water was the cause of ill health of the urban population and it had a direct impact on the economic health of the country. He brought the sanitary idea and resulted in remarkable improvement in the health condition of the city.

Legislation in Public Health in Nineteenth Century

Gradually State realized Health is a state subject and GOVT has to act to ensure his people otherwise there will be direct fallout of economy. So Europe, USA, and then different colonial countries passed different legislation and set up different boards and commission for further implementation of health policies. Such as "reporting of dangerous diseases to authority act", "immigration act", "Food inspection act", "recording of Birth, marriage and death act", set up of the sanitary commission, placing surgeon generals for controlling different endemic and epidemics were given a jolt in public health approach. But the approach of implementation of acts and motive was different

between ruler country and colonial countries. So initially there was huge resistance against these acts, and against the epidemic act in India 1897, riots flared up in Mumbai, Delhi, and Lahore.

Organized Research in Public Health :

With the establishment of different universities with a focus on public health, organized research also got a boost. In 1948 Richard Doll Bradford Hill conducted a study on the etiology of Lung Cancer. They identified smoking was the leading cause of Lung Cancer. This study not only identified Lung cancer as an important etiology but successfully made a landmark for **Case-control study** , which is considered until now as a pivot in epidemiology. Gradually Public health approach extended to Noncommunicable diseases also. In 1948 Framingham's study began with the goal of identifying factors that contribute to developing cardiovascular diseases.

Due to the advancement of Research, Medical education, Immunization, Sanitary systems there was a significant decline in mortality and morbidity in the mid-twentieth century. In 1959 Rene Dubos in his landmark book " **The Mirage of Health**" written that decline of mortality since 1850 was not primarily due to laboratory medicine, it was due to control of infectious diseases, improved sanitation, and nutrition.

History of Healthcare in ancient and medieval India :

Aryans brought with them, their own Gods, agrarian practices, and Vedas. These Vedas were believed to be the guiding principles of life and hence were riddled with Shlokas containing hymns and prayers for not just a healthy body but a healthy mind. Indians even had a God of healing known as Dhanvantari.

Ayurveda was the science of long life. Charaka, from King Kanishka's court, is known for writing down one of the earliest books on medicines sciences, the first detailed healthcare work in India which also described complicated surgical procedures. Charaka's efforts in establishing a healthcare system led to the development of two schools of healthcare i) Surgeons, and ii) Physicians.

With the rise of Buddha and his beliefs, invasive healthcare procedures were discouraged, as they were viewed as "himsa" on the body, which came in conflict with the Buddhist principle of "ahimsa". It is believed that Buddha himself tended to the sick. The focus during this period was on healing the inner energy/ soul/atman to heal the body.

In the more recent ancient history notes, it is believed that King Ashoka had developed the most comprehensive healthcare system under his reign. It is interesting to note that his reign extended from present-day, Afghanistan in the west to present day Bangladesh in the east. It is believed that King Ashoka established many hospitals in his empire; these became centers for healthcare and wellness.

With the advent of Muslim rulers, Ayurveda was pushed back as the Muslim rulers preferred their own Unani practitioners. King Akbar was one of the few rulers who saw the benefit in combining practices of both Ayurveda and Unani medicines to develop a better healthcare system.

The Indian healthcare system took a decline as the Mughal period took a downfall; the knowledge of the past was devoid of its scientific rigor and fraught with myths about diseases. It was at this time that the Church and its brand of medicines entered the Indian subcontinent.

Public Health in British India :

When Europeans came to India, they faced a challenge as India was having different endemic diseases in different parts of the country with episodes of the epidemic.

It is quite interesting to note that the first modern hospital in India was established by the Portuguese in 1510. It was known as the "Royal Hospital" however, the real revolution in healthcare practices was brought by the French and British colonists; especially, the British who built their first hospital in Madras in 1667, followed by more hospitals at their centres. These hospitals were initially created to provide better healthcare to British officers who were posted in India. They aimed to serve their own community preferentially and to prevent the spread of diseases from India to Europe with returning soldiers. To create more human resources from natives to meet demand they established medical colleges in several parts of the country – Calcutta Medical College -1835, Lahore Medical College -1860. However, from 1859, the British Crown took many steps in ensuring that healthcare was more inclusive. Observing a high rate of mortality among British soldiers Royal commission recommended sanitation in every presidency which took formation in 1864. Vaccination against smallpox started much before in British India -1802. Major epidemics in the nineteenth-century were Smallpox, Plague, Cholera, and Malaria. As a part of the International Trade route, there was immense pressure on the British Government to control emergencies. So, British Government passed the Epidemic Disease Act 1897 to implement necessary measures to control the epidemic. But Colonial power was used vigorously to

execute. Human emotion, sentiment, racial, religious issue relevant that time India was not taken into consideration. This gave birth to resentment and riots flared up in different parts of the country.

In the nineteenth-century British Government started the establishment of railways, construction works, irrigation works, without keeping in mind of sanitary and drainage works. This had lead to the flare-up of Malaria. Thanks to Dr Ronald Ross who discovered the life cycle of Malaria for which he got Nobel Prizes in 1902. This discovery gave a new horizon in eradication malaria with mosquito control. It should also be remembered, that healthcare provided to Indians was only to ensure their survival and health so that they can continue working for their British masters, which meant that bare minimum resources were spent on the second class citizens of the British Empire.

"In this unfortunate country we have never had public health services in the sense in which they are understood in the West. We have a few hospitals and dispensaries , hardly one for a taluka , considering the vastness of the population. We have no facilities for the curative and preventive side of disease. ..... No country in the world is medically so badly served as India because the Government never considered the health of the people as its first and foremost concern and its national wealth, as much as it considers law and order and the police and the military to be."

— JIMA , April , 1946

In spite of these, formation of Bhore Committee in 1943 was a major breakthrough in development of Public Health System which made back bone in Independent India.

Public Health in Independent India :

Along with its freedom, India inherited a crippling economy, booming population, and a deep healthcare crisis.

The total deaths amongst children under 10 years, as a percentage of total deaths at all ages was 48·4 in 1937, about 200,000 women die every year from diseases and conditions associated with pregnancy and child bearing. The average number of deaths during 1932-41 from cholera was 144,924, from small pox 69,477, from plague 30,932—all preventable diseases. There are about 2·5 million tuberculosis patients in an infective stage in the country and there is only a total of 6,000 beds to provide facilities for their isolation .....

..... The average diet is ill-balanced, lacking in calories, salts, vitamins and protein. Famine and prefamine conditions are general.

Editorial, JIMA, August, 2020, P-10

Before India's independence, a 20 member committee was formed headed by Sir Joseph Bhore. The Bhore committee conducted the first-ever and probably the most extensive probe into the healthcare system of India then. The Bhore committee discovered that the availability of hospitals in India was 0.24 per 1000 population. The committee made several suggestions for improving the healthcare system in India, however, within a year of the submission of the said report, the British emperor, exited India forever.

The first Prime Minister of independent India Pandit Nehru realized the need for improved healthcare for the building of New India. Even before Independence in his report in 1928 public health was viewed as a constitutional right. It was the first draft constitution in Pre Independence period.

He did not forget to put health as an important determinant in democratic India and role was clearly mentioned in Constitution placed in Indian Parliament By Dr B R Ambedkar. Article 39(E) of the Indian Constitution contains an important provision related to public health: Article 47 places a duty on the state to raise the nutrition levels and standard of living of people of India, consider public health as a primary right for worker's health, women, and children.

Two five years plans, following independence, had allocated INR 770 crore to develop healthcare but not to avail. By the third the five-year plan, the then government decided to conduct another study on understanding the healthcare problem in India.

In 1959 Dr. Mudaliar Committee recommended strengthening of District Hospital and the formation of different Health Programme for the eradication of Malaria, Leprosy, Tuberculosis, Smallpox. Chaddha Committee was made to further strengthen the Malaria eradication Programme. In a significant move in 1966, a new committee was formed headed by Mr. B Mukherjee to review existing health programs. Mukherjee committee studied the Mudaliar and Bhore reports, along with the Healthcare Act of 1935, through its understanding of the acts and reports and their shortcomings, this committee led to the development of the new model of healthcare in India which was a structured strategy involving ground workers, PHCs, tertiary Care Centres and urban Hospitals. Kartar Singh committee has given the recommendation for institutional delivery, family planning, and nutrition. Srivastav Committee in 1974 recommended planning for medical education.

Public Health in Modern India :

Modern India has two face – India and Bharat . On one side there was a rapid advancement of Technology,

foreign Investment in health, urbanization, Industrialization and increased demand for upgraded healthcare facilities. On the other hand as a byproduct of urbanization, deforestation there was an increased incidence of zoonosis (emerging and reemerging infections), vector-borne diseases (due to poor sanitation and drainage), an exponential increase of Noncommunicable disease (Diabetes, Hypertension, obesity), and mental illness. Urbanization also led to a gradually increasing disparity among the poor and the rich population. This led to an increase in the slums and deterioration in the sanitary conditions which further heralded to the increase in the number of communicable diseases. Since the nineties, there has been a decrease in the ratio of doctors to the general population which led to a delay in the presentation of the patients to the health care system.

National Tuberculosis Programme was restructured as RNTCP from 1997 which was characterized by direct observation of therapy by health workers. There was a significant reduction in failure rate in Tuberculosis with improved compliance. GOI took an ambitious project at 2017 to END TB by 2025.

NACO was formed in 1992 in the face of HIV an emerging epidemic. Prevention, creation of awareness, and treatment was three primary Goal.

The malaria control program was renamed as the 'National Vector-borne Control Programme' in 2003 to bring all vector-borne control programs under one umbrella.

National Health Mission was formed in 2013 to form a link between community and health system through the Accredited Social Health Activists(ASHA), Health Care Contractors providing facilities of Janani Suraksha Yojana, National Mobile Medical Units, Janani Shishu Suraksha Karyakram, Rashtriya Bal Swasthya Karyakram, Tribal TB Eradication Project and National Iron+ Initiatives to the community.

In a significant move GOI taken initiative "Swachh Bharat Mission" on 2nd Oct 2014 to achieve an " open – defecation free" and eradication of manual scavenging

"Sanitation should not be seen as a political tool, but should only be connected to patriotism and commitment to public health."

To meet the demands of the affordable societies, the government boosted the corporate sectors to invest in health care facilities having high technology with high cost. Medical Education was also restructured with the encouragement of setting up more medical colleges with increased undergraduate and postgraduate seats. As the public sector was not capable of the meeting making the ends meet, the government turned to the corporate sectors for help.

But there is a darker side also, which is not beyond criticism. Unfortunately, the focus has been shifted in modern India. Some imbalance appeared between the Public Sector and Private Sector. The government of India gradually moved towards a Hospital-based Public health approach rather than involving mass. The shifting of Focus further deepened after 1990 particularly when GOI adopted an open market policy. Model Public health policy which was adopted in 1950, though rectified in 1987 yet to implement by most of the states. So the focus was more on the curative aspect, rather than preventive, more on hospital-based service rather than community-based service. So also changes came in Medical education also. Boosting of private enterprises, insurance-based policy, more and more super speciality focus deepened the crisis. The Public Health sector was neglected and so there was an increased incidence of both communicable and non-communicable diseases. The high cost of illness, disability, and death put Indian society in a crisis, particularly the poor was the worst sufferer. Also, profit driven Corporate sector attracted Medical Professionals more towards its curative and technological-based practice which is financially more lucrative.

"We are not against private health care, but it shouldn't take the place of public health care services. Relying too much on private medical care, without the availability of public health services will allow exploitation of under-informed patients and their families, because of the asymmetric nature of healthcare knowledge,"

— Amartya Sen

There were several outbreaks of different epidemics, but the lack of modern infrastructure to combat diseases more in a field of Communicable diseases lead to a helpless situation to the Government and People. It became grossly exposed during the COVID pandemic. Having such lacking, Govt tried to adopt the old method of controlling epidemic – quarantine, and lockdown. But these strategies are not beyond controversy. On one side restricted freedom, and on the other hand, the gross economic fallout which is crucial for the poor, who become poorer. In India, there is gross apathy in maintaining the database, making difficulty in determining Health indices for proper health planning. Indians often rely on western data for formulation health strategy, which may not be appropriate in the Indian context. The problem further intensified due to social, cultural, economic, environmental diversity. Health planning or policy cannot be uniform across the whole country. Decentralization should be the rule in the Indian public health approach. The public health

approach in India is hospital-centric, health planning is concerned more with the health of health care services than the actual health of people. The remedy was sought in terms of different control programs again those were implemented through hospitals. Control Programmes have shown success but often ended with poor maintenance.

Medical Education and Public Health :

The British Govt realized the need for huge trained health care personal in this country. To fulfill the gap that time Colonial Govt established Calcutta Medical College in 1835. Gradually a few more colleges opened but the curriculum of Medical education formulated. Indian Medical Services introduced in 1896 to create health care administrators. School of Tropical Medicine in 1922 and All India Institute of Health and Hygiene in 1932 aimed at basically to control epidemic and endemicity of Communicable diseases. Public health and medicine have been mutually dependent and interact with each other. So Health education and Medical education should have interplay at a certain point in time. With the establishment of the Medical council of India in 1934 medical education got a jolt. Post Independence GOI had taken several steps to boost Medical Education, still, there was a gap in the public health approach by medical graduates. So in ROME program launched in 1977 for the adoption of preventive, promotive, and curative health care in the community.

Development of International Health Agencies :

Unicef was formed in 1946 aiming to alleviate poverty, good health, and wellbeing of children and mothers, education, removing gender inequality, and improved sanitation. WHO was established on 7th April, 1948 was a major breakthrough in the history of the Public Health of World. The aim was universal healthcare, monitoring public health risk, coordinating responses to health emergencies, promoting human health, and well being.

Vaccination and Public Health :

Vaccination is an important tool in the Public health care model. Tribute to Dr. Edward Jenner 1796 who brought the concept of vaccinology. In annals of Medicine in his article " inquiry into the cause and effects of the variola Vaccine," he had written " Cowpox protects the human constitution from the infection of Smallpox". Subsequently in nineteenth-century vaccination against rabies, Plague, Cholera discovered. In the twentieth century there were significant advancements in the discovery and implementation of vaccines. With the formation of WHO, UNICEF, ROCKEFELLER FOUNDATION world moves towards a universal Immunization program (EPI by WHO in 1974). There was significant decline of few killer communicable diseases like Polio, Diphtheria, Cholera, Whooping cough e.t.c. More significantly in 1979 WHO declared the world is free of smallpox. But in Twenty-first Century there are emerging and reemerging of few infections.In this century there is a significant advancement in technology, but political will and investment can only bring a new dawn in the prevention of communicable diseases. In the COVID pandemic, there is a rat race to launce Vaccine by different countries to grasp the market as early as possible. If the economic agenda dominate over the social issue, it can not serve the best, as there is a chance of deprivation of poorer countries because of less affordability. For any infection, it is the universal coverage that can only eliminate the virus.

Poverty and Health :

Poverty is a major cause of ill health and a barrier to accessing health care when needed. This relationship is financial: the poor cannot afford to purchase those things that are needed for good health, including sufficient quantities of quality food and health care. But, the relationship is also related to other factors related to poverty, such as lack of information on appropriate health-promoting practices or lack of voice needed to make social services work for them. Ill health, in turn, is a major cause of poverty. This is partly due to the costs of seeking health care, also due to the considerable loss of income associated with illness in developing countries. This issue surfaced during the COVID pandemic in Migrant labor issues. Poverty forced migrant laborers to stay in congested rooms , taking less nutritious food and lead to spreading disease from one to another.

"Poverty is the greatest polluter"

— Mrs Indira Gandhi, 1972

This proves the Public health approach is multidimensional. Economical health of an individual or community is essential for the successful implementation of Public health Programmes. So also education. Otherwise, all beautiful efforts will be looked like a fried Roti.

ক্ষুধার রাজ্যে পৃথিবী গদ্যময়
পূর্ণিমা চাঁদ যেন ঝলসানো রুটি

— Sukanta Bhattacharya

Religion and Public Health :

The Kurma Purana states that taking the *pratah-snana* [bath before sunrise] makes one *namohsuchi*[pure] and allows him to perform duties such as japa, homa, and Deity worship. If a person eats without having bathed, he is said to be eating

filth. *Pratah-snana*is compulsory for all, except those who are ill. In Vedic culture bathing is considered a sacred act to be accompanied by meditation on the Lord and recitation of prayer. A bath can purify even a sinner, for it has the power to wash away all external and internal contamination. Even the Qurans have stated that, cleanliness leads to the state of "Fitra" or "fitrah" (Arabic: فطرة ; ALA-LC: fimrah) which is the state of purity and innocence. But during the Medieval times, religious outlook started dominating over the society's thinking and policies leading to its distortions like practising child marriage, avoiding family planning and avoiding taking immunisation based on religious beliefs alone. With the advent of European Renaissance, exploration of freedom of thinking and scientific thinking took place which had a very positive impact on the public health care.

Health and Economics :

Productivity can be boosted by a demographically young population if we can protect them from ill-health. Education and health can generate a diversified workforce that can be an asset of a country. There is robust evidence that investments in public health can pay rich economic dividends. WHO Commission on Macroeconomics and Health (2001), two other economists-led reports on Investing in Health (1993, 2013) concluded that investments in public health will generate rich returns and ensure economic growth.

After the 1990s, there is economic growth in the country, increase GDPs, investment in service sectors, urban sectors, trade, but health investment is preferentially in private sectors that are mostly focussed on technological based super speciality services. Govt spending in Primary health care system or Public health is less than 1.2 % of GDP. Average spending in the Health sector in developed countries is around 8.8% of GDP . This proves Public health is the least priority in India,

"India can boost in human capita's productivity by investing in education and Healthcare"

— International Monetory Fund (IMF)

Questions may be raised as to how this can be done at a time of economic crisis. History teaches us that such an investment may be useful in times of economic adversity. South-East Asian countries invested in health and universal health coverage during and soon after the Asian Financial Crisis of the 1990s. The United Kingdom adopted universal health coverage soon after the Second World War. Japan invested in the early 1960s for recovery from the economic crisis that happened by defeat in that war. All of them recognized that better investment in health is a winning tool for economic development. India too should follow the path to boost the trajectory of its economic growth.

At the bottom of Pandora's box lies hope. COVID-19, which emerged as a curse of our physical, economic, and social life, will fade away with time. We can only regain our glory If we embrace our old proverb "Health is Wealth".

"Economic Growth without investment in human development is unsustainable andunethical"

— Amartya Sen

All efforts will go in vain if we cannot create vibrant, enlightened, committed health care workers – including Doctors, Nurses, Paramedical staff, public Health. administrator a dedicated Public health Specialist with good remuneration (including insurance for death or disability), satisfaction, and pride in the profession. Separate Fund allocation on Public heath, the building of infrastructure, and Human resources should be a priority. There should be a strong surveillance system that can exactly detect or predict an outbreak. India has an Integrated Disease Surveillance system (IDSP) but needs a stronger commitment with legislation to meet any challenge. Updated Epidemic act should give doctors enough power even above bureaucracy to achieve clinical significance rather than statistical significance. Lack of transparency, rumors in public (today at social media), unbalanced media reporting hinder epidemic control in times of crisis. We should not repeat mistakes of the past and should be prepared with a better epidemic act that will incorporate human emotions, participation, preserved fundamental rights. Pandemic provided us with a break from the past and an opportunity to relook our approach.

"We should make a trust based Public health system and new Pandemic act that include People's sentiment , involvement and confidence suitable for an Independent, democratic country which will not repeat the mistakes of colonial period."

JIMA, Editorial, May 2020

So in my opinion, this pandemic has given us a wake-up call for a long walk to build a stronger and trust-based Public healthcare system in India.

"He gives his harness bells a shake
To ask if there is some mistake.....
And miles to go before I sleep
And miles to go before I sleep"

— Robert Frost

From Archive

JIMA, JANUARY, 1946, P-122

JOURNAL OF THE

INDIAN MEDICAL ASSOCIATION

CALCUTTA, JANUARY, 1946

LEGISLATURE AND THE MEDICAL PROFESSION

India is a subcontinent of 655,000 villages. Over 90 per cent of its 400 million inhabitants live in and around the villages. While modern towns and highways have sprung up here and there, the villages are still in their old state, where approaches are difficult, environs are filthy, houses are badly planned, water-supply is primitive and inhabitants are the prey of small-pox, malaria, cholera, plague, leprosy, skin diseases and other affections. Visitors to our country and even our own countrymen have described the situation in gruesome tales. Some have blamed the villagers, and others the Government. But the fact remains that poverty and illiteracy are the main causes of this backwardness for which the villagers themselves are hardly responsible. The public health measures which had been introduced from time to time by the Government were scrappy, unimaginative and invariably were sacrificed in the end at the altar of finance.

To serve these 400 million there are about 40,000 doctors or 1 to approximately 10,000 people. Inspite of this low figure we find unemployment and crowding of the profession in the urban areas. We discussed this problem some time back. It is estimated that about 300,000 doctors are necessary for proper medical services to the people. From a recent summary of the Bhore Committee's Report published in the press we gather that it has recommended to provide one doctor for 2000 people. It also envisages to establish treatment centres in the villages with the help of local committees whose co-operation is considered to be essential for the success of the scheme. We hope to discuss this scheme in detail in future. Scientific medicine has made good progress in our country inspite of its illiteracy and low economic level. The benefit of scientific medicine can be made available on a wider scale to the people, if it is made cheap simultaneous with the intense activity of the public health department. It is a good sign that people have become health conscious and demand living wages, better housing, nourishing food and medical benefits. During 1939-41, the Government expenditure on public health was about 1*d*. (an anna is just over a penny) per capita in Madras, Bengal, and the Punjab and about 2*d*. in Bombay. This lamentable lack of public health in our country is a fact beyond dispute and one has only to look at the mortality figures from communicable diseases to confirm this. In one or two provinces the public health services are worse. The Famine Enquiry Commission came to the conclusion that Bengal Public Health services were not only 'insufficient to meet the normal needs of the population' but also that 'the level of efficiency was below the standard of certain other provinces'. Although public health was a transferred subject for the last quarter of a century we fail to understand why so little could be achieved so far except adopting stop gap and tinkering measures here and there.

It looks to us that time has arrived when the medical profession should ventilate the urgent necessity of public health measures for our country in the legislatures. It is unfortunate that so far the members of the medical profession have betrayed a sort of mental apathy and taken no active interest in seeking election to the legislatures and other local bodies. They have missed the opportunity of guiding the legislature along the right line and thereby focussing public attention on urgent reforms on public health problems. In England, the British Medical Association not only set up candidates for Parliamentary Committees but also finance their election expenses. In the last general election, a fair number of doctors have been elected on labour ticket. Now that the Selection Committees of the various political parties are busy in selecting their candidates to the Provincial Legislature, would it not be wise for them to select some competent medical men from the profession, who have given thought to the medical problems confronting the country?

The duty of giving effect to the recommendation of the Bhore Committee will naturally fall on the provincial legislature. Whichever political party dominates in the provinces, public health should be treated above party politics. It will be the duty of the medical men in legislatures to enlighten the house on the need of such efforts. At present dyarchy rules over the public health administration of the provinces. The Ministers-in-charge of the Public Health portfolio have been non-medical men advised by the departmental heads of the Government, the Surgeon-General and the D.P.H. The District health officers are in the employ of the local bodies and the D.P.H. has no control over them and no power of selection or transfer. Much improvement is needed in the above administrative machinery before any health programme is launched in order to bring any progress in the health of the people.

LATE CAPT. P. GANGULY

In another page, we publish an obituary note of Capt. P. Ganguly. He was associated with us as Assistant Editor from 1939-41, when he endeared himself to everybody for his sincerity, erudition and devotion to work. In his death the profession has lost an eminent member and the public a sympathetic physician. We pray to God that his soul may rest in peace.

From Archive

JIMA, Vol. XV, No. 7, APRIL, 1946

independence, the G.M.C. would hesitate to raise the old silly objections and not only continue but extend the reciprocity.

Forward Steps Needed

In accordance with the spacious times ahead of us, we shall have to make some forward moves, sorely needed to keep pace with the demands on our profession. We must have a central office at Delhi (not in Calcutta) with a paid secretary and a weekly paper of our own. The central location is suggested as we have to establish so many contacts with the popular government at the centre and with the autonomous governments in the province, and speak in the name of one association and with one united voice. In the medical life of the country we should exercise the same influence as does the Congress in the political life. Nothing is done and achieved in this world without organisation and hard thinking. With the undoubted influence of the profession with the people, rich and poor, and with subscriptions of our own fraternity, it would not be at all difficult, I venture to say, to raise the necessary funds for the habitation of the central organisation at Delhi.

Our full time paid secretary will have plenty of work to do in organising the profession. The Congress with the office at Swaraj Bhawan in Allahabad deals with the administrative work of a vast organisation, and as our profession is also countrywide and will expand with the times, it is most urgent to have the building and the staff.

Our monthly journal is in need of becoming a weekly paper. The need of medical knowledge is much greater and it can be better served by means of a weekly rather than a monthly journal; and our profession has more journalist-doctors who know how to produce a smart weekly. Our paid secretary will supervise the work of this weekly. I feel it will pay its way, and may show even a profit in the course of time, as the thirst for medical knowledge and discussion is keener to-day than ever before. Let us appoint the paid secretary, give him the staff, rent a house at Delhi by transferring ourselves from Calcutta, and very soon we should achieve the ambitions of having our own building.

Quackery

Quackery is a subject which is a hardy annual at our meetings. The whole subject has been exhausted in writings and speeches. But the more it is condemned the more it seems to be thriving. I need not dwell upon its horrible evils. The paucity of qualified doctors and the poverty of the people are the cause for the existence of the quack. The population of the country is increasing rapidly and some one or other has to be found to give even a quack's treatment.

But those who practise, what goes by the name of the Western system of medicine, have a right to demand protection against the quack. He is reckless in Allopathic treatment. He is not deterred by the law; and he treads on ground where even the devils fear to tread. Some relief from quackery can be given by government by a few simple rules:—

(*i*) no medical practitioner shall be entitled to affix the word 'Doctor' before his name unless he is a registered practitioner in Western medicine;

(*ii*) no person shall be entitled to prescribe drugs which are in the British pharmacopœia, specially injections and poisonous preparations unless he is a registered medical practitioner;

(*iii*) those who practise the Unani and Ayurvedic systems of medicine may style themselves as "Hakims" and "Vaidyas" as the case may be.

There is need in this country for dealing as early as possible with the whole question of quackery. Our Medical Association can take up this question, draft a Bill, circulate it for opinion, and have it introduced through some of our doctor friends in the provincial legislatures. Better still, we must mobilise opinion in every province requesting Government to undertake such legislation itself, as quackery is a public danger and should no longer the tolerated.

The Health Survey & Development Committee (Bhore Committee)

We of the All-India Medical Conference are most vitally interested in the recommendations of the Health Survey and Development Committee (Bhore Committee), whose report has been signed and will shortly be published. It is a document of the utmost importance for the promotion of the public health of British India as a whole, and, I have no doubt, that the Indian States will find much in it of the highest value for their own guidance. In their letter while appointing the Bhore Committee the Government of India have asked them to "plan boldly, avoiding on the one hand extravagant programmes, which are obviously incapable of fulfilment, and, on the other hand, halting and inadequate schemes which would have no effect on the general health standards, and which would bring little return for the expenditure involved."

The Bhore Committee's task was two-fold. It had to produce a sufficiently good scheme for the whole country on which the future health services could be firmly based, and also to bring the cost within the country's financial means—a very hard task to be set before men, who had to think first of straw before they could make bricks.

In this unfortunate country we have never had public health services in the sense in which they are understood in the West. We have a few hospitals and dispensaries, hardly one for a taluka, considering the vastness of the population; we have no facilities for the curative and preventive side of disease; and hardly 10 to 15 per cent of the people have ever received the benefits of modern scientific treatment. Men die like flies of epidemic diseases because there are no organised medical and health services, and relief is only spasmodic. Hardly three annas is spent per head of the population by way of medical relief and sanitation, whereas in Great Britain they spend Rs. 54 per head and in the United States about Rs. 51. No country, in the world is medically so badly served as India because the Government here never considered the health of the people as its first and foremost concern and as its national wealth, as much as it considers law and order and the police and the military to be.

These are days of planning all round for economic and social amelioration and blue-prints are being pre-

Review Article

Proposal for an Affordable and Sustainable Universal Health Cover Model for India : LAN, WAN and SAN

Umesh Gupta[1]

A unique model of Universal Health Cover in India is proposed for funding by government and service delivery by private generalist doctors. This model contrasts with the current government schemes of funding only in-patient services by the private sector and ignoring primary health care as an overall cost-reduction strategy. The current government schemes rely on public facilities to deliver out-patient services, even while 70% of such services are availed from private practitioners. The proposed model would have been highly effective in the current Covid-19 crisis and will enable a much more robust response to future pandemics and other disasters.

Local Area Health Networks (LAN) are proposed, based on residential pin codes, comprising of private generalists, public facilities, and diagnostic centers. The beneficiaries of the model would be able to obtain services from within the Local Area Health Networks and refer to designated hospitals only for in-patient services. Virtual Local Area Health Networks (VLAN) are areas without the health services and these areas van be attached to LAN. Legislative assemblies define the boundaries of Wide Area Health Networks (WLAN) that link up LAN and VLAN for integrated professional management of healthcare. A group of LANs can lead to a tertiary care provider to create Systems Area Health Networks (SAN) for super-specialties.

Payments are proposed to be made on a Prospective Payment System based on Diagnosis Related Groups and accounting for geographical variations, with incentives for clinical quality.

The cost of the proposed model for 100% Universal Health Cover is estimated to be about Rs. 11,369 crores for out-patient services and Rs. 28,896 crores for in-patient services. The estimates are based on a detailed analysis of data from the 75th Round of NSS Report and case-mix costing has been applied.

[*J Indian Med Assoc* 2020; **118(9):** 20-5]

Key words **: Universal Health, Case-mix, Prospective Payment System, Diagnosis Related Groups, Primary care**

With the latest Government scheme of health cover, 50% of Indians will still be without any health insurance coverage and will pay out-of-pocket for their health needs. Even these extremely vulnerable population will still have to pay for out-patient services. The policymakers have relied on public facilities for such needs, ignoring the fact that public facilities are availed by less than 30% of the patients in both rural and urban populations. In-patient services are far more expensive and benefit only a few. Out-patient services achieve meaningful positive health outcomes and prevent hospitalizations, thereby creating a sustainable Universal Health System.

A unique Indian model of Universal Health Cover is proposed based on an analysis of the health insurance and services utilization. This model also draws upon the benefits of other socialist health systems of the

Editor's Comment :

- The current government health schemes provide for in-patient services only and that too for only the extreme vulnerable
- The government policies ignore the fact that population health is achieved by adequate out-patient health services that prevents hospitalization
- The policymakers rely on the public facilities to provide the out-patient services
- However, 70% of out-patient and 45% in-patient services are availed from the private sector
- A unique model of Universal Health Care in India is proposed for out-patient services delivered by private generalists and funded by the government
- Both, the out-patient and in-patient services, can be organized into Local Area Networks (LAN) based on residential pin codes and legislative assembly seats respectively
- These can be governed by creating Wide Area Networks (WAN) based on Legislative Assemblies
- Such an organized national health service would have been invaluable and highly effective in the current pandemic

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Received on : 10/06/2020
Accepted on : 19/06/2020

UK, Canada, Australia, and Europe. All mature health systems have defined the "clinical product" for "purchase" by using the Diagnosis Related Groups (DRG) system[1]. The DRG system has also been supported by WHO as the way forward for healthcare financing[2]. A Prospective Payment System (PPS) based on Diagnosis Related Groups (DRG) is also suggested.

The Current State of Healthcare :

Health Insurance Coverage in India[3] (Fig 1) -

Despite 70% of out-patient services and 45-55% in-patient services availed from the private sector, only in-patient treatments are covered by any of the current Government schemes as well as by private insurers. About 35.71 crore Indians (27.5%) are now covered by some governmental schemes for in-patient treatment in private facilities[4]. The covered population is aimed to expand to about 50 crore Indians with an increased enrollment for the Ayushman Bharat Pradhan Mantri Jan Arogya Yojna (AB-PMJAY) scheme.

Government Schemes :

1. AB-PMJAY Scheme – Aims to cover approximately 50 crore beneficiaries of which approximately 4 crores have enrolled with e-cards. There is a limit for in-patient treatment up to Rs. 5 lakhs at government-approved rates in the private hospitals. Most private hospitals have resisted the scheme as the rates are arbitrary and unsustainably low.

2. Central Government Health Scheme (CGHS) – covers 34 lakh beneficiaries of central government employees and dependents.

3. Employees State Insurance Scheme (ESIS)– covers 2.3 crores employees,and their families, in private or public employment. This is an employee contributory scheme and the reimbursement rates are similar to CGHS rates.

4. Ex-servicemen Contributory Health Scheme (ECHS) - provides cover for retired personnel of the armed forces and their dependents.

5. Rashtriya Swasthya BimaYojna (RSBY) – provides cover for 36 lakhs beneficiaries. Only in-patient treatment up to INR 30,000 at government-approved rates is covered.

6. State Health Insurance Schemes – Rajiv Arogyashree, Vajpayee Arogyashree, Chief Ministers Comprehensive Health Insurance, etc. for Below Poverty Line (BPL) populations. These are to be subsumed into the AB-PMJIAY scheme.

Non-government insurance: approximately 11.5 crore Indians (8.8%) have a non-government sponsored insurance cover. This includes:

1. Group Insurance Schemes – providing cover to 7.29 (6.1%) crore beneficiaries
2. Individual Insurance – with 4.21 crore (3.23%) beneficiaries

Uninsured : about 82 crore Indians (63.7%) still do not have any form of insurance and pay out of pocket. With the expansion of the AB-PMJAY scheme, this will decrease to 67 core Indians (51.5%) still without any form of insurance cover.

Service providers : The private sector provides almost 70% of the health services in both urban and rural India. The strong public health systems in countries like the UK, Australia, and Canada deliver primary care through private practitioners only. The primary healthcare in these countries is publicly funded but privately delivered[5]. Experience from Liverpool and the UK NHS Trust system shows that better public health outcomes are achieved through integration with primary care, which is delivered by private practitioners[6].

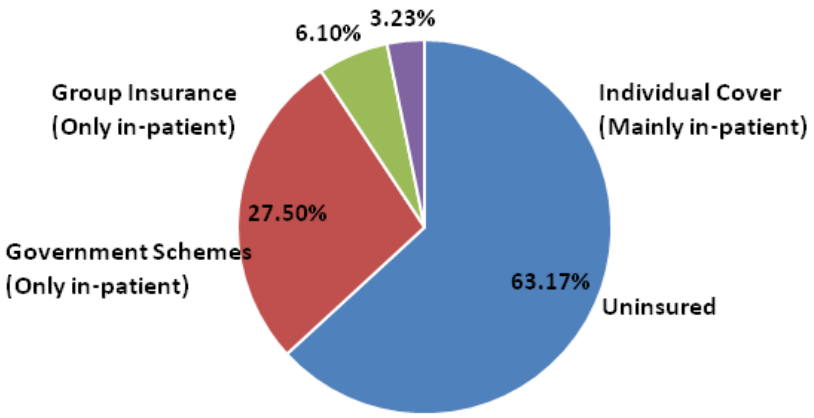

Fig. 1: Health Insurance Cover in India

The Volume of Services : The proportion of persons reported as ailing (PPRA) within the last 15 days was 6.8% in rural and 9.1% in urban areas[7]. Of note is that only 30% of patients avail public health facilities in both areas. The average cost of out-patient treatment per episode in rural areas was Rs. 325 in public and Rs. 566 in private clinics. The corresponding cost in urban areas was Rs. 344 and Rs. 714 respectively. Medicines comprise 70-82% of these costs, 11% for diagnostic tests and 7-19% as

doctor's fees[7].

Of the 749,272 hospital beds in public facilities, 65% are in urban areas[4]. The Majority of the 1,021,000 bedsin private facilities are in urban areas[8]. As per the 75th NSO data, within the last 365 days, 26 persons per 1000 population in rural and 34 persons per 1000 in urban areas availed in-patient treatment. About 46% in rural and 35% in urban areas was delivered in public hospitals where the cost of treatment was Rs. 4,290 and Rs. 4,837 per episode[7]. However, these figures are only for drugs not available and minimal user charges (if any). Most of the costs in public facilities are funded by the government and are not charged to patients.Hence,cost differences cannot be interpreted as cost-effectiveness differences.

Most people avail of services from private practitioners and facilities due to ease of access, the reputation of the practitioner and/or the ambiance of the setting. A rapidly increasing and unwanted trend in urban areas is of patients seeking specialists for even the most banal of ailments in the expectation of rapid relief or perceived competence or the internet.

Proposed Model of UHC in India :

This model proposes for publicly funded out-patient and in-patient services to be delivered by private generalists and hospitals, organized into defined referral pathways (LAN, WAN, and SAN) based on residential pin codes and legislative assembly seats. Beneficiary categorization, disincentives, and strategies for misuse prevention are also suggested as below.

Local Area Health Networks (LAN) (Fig 2): Based on the 19,097 pin codes in India, each LAN will have an average of 68,000 people. The LAN will comprise of registered private clinics, diagnostic centers, public dispensaries,and secondary care hospitals within that pin code. Public patients can avail services only from the LAN of their residential pin code. Similarly, generalist doctors can register only one clinic for public services.

Generalists are expected to be gate keepers for referrals to specialists and in-patient services. Patients in the affordable category will continue to visit the out-patient and in-patient doctor of their choice by utilizing their private insurance or pay out-of-pocket.Computer software can enable a fair distribution of referrals to the hospitals that can provide the clinical services needed, either within a LAN, WAN or a SAN.

Fig. 2: Local Area Health Network (LAN)

Virtual Local Area Health Networks (VLAN) – Pin codes that do not have doctors or diagnostic centers can be designated as VLAN and these areas can be tagged to a LAN. The advantage of designating an area as a VLAN is that special schemes and policies can be designed for these areas for attracting health service providers. LAN providers could be permitted to operate another facility in a VLAN, apart from their facility in a LAN.

Wide Area Health Networks (WAN) – will link up all LAN within a legislative assembly area for management and governance of the system, complaints resolution, and quality monitoring. The elected MLAs can also be involved in the management of WAN by creating a public governance Board for each WAN.

System Area Health Networks (SAN) (Fig 3) –

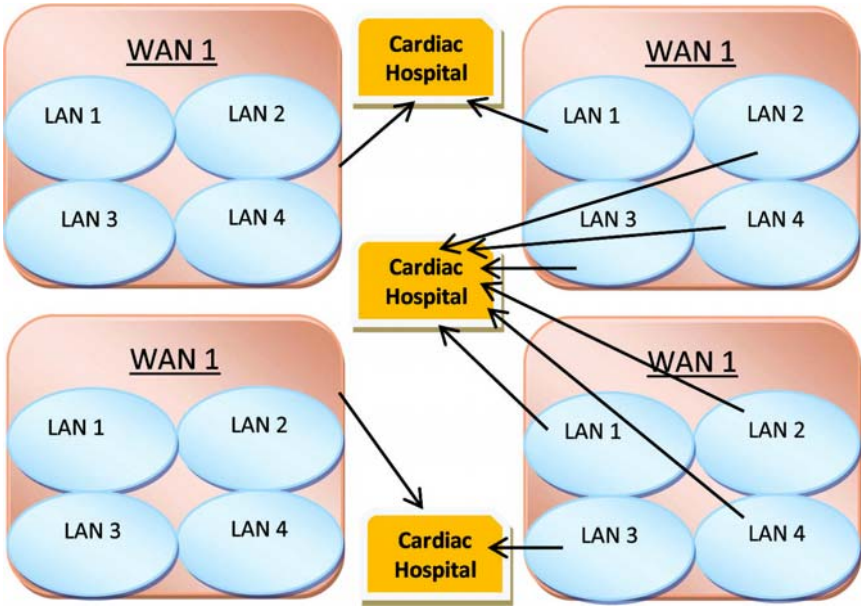

Fig 3 — LAN, WAN & a Cardiac SAN

tertiary care facilities such as interventional cardiology, neurosciences, nephrology, and cancer services are fewer and concentrated in big cities. Some tertiary care facilities are specialized in a single super-specialty. Hence, System Area Health Networks (SAN) can be created for each of the specialized services and LAN linked to the SAN. Computer software would drive the fair distribution of referrals, stamping out the current referral practices.

Beneficiaries (Fig 4) – Universal Health Cover by definition includes all citizens and permanent residents of India. However, healthcare recipients can be categorized as Public or Private Patients at the time of service delivery. Private patients are those who have the means to fund their healthcare and can be identified based on earnings and ownership of luxury items such as a car. Public patients (UHC beneficiaries) can be further categorized as "Vulnerable" and "non-vulnerable". The vulnerable group is the same as the recipients of the current AB-PMJIAY government scheme. Disincentives for availing UHC benefits could include:

1. No choice of the service provider. Beneficiaries would be treated by a designated service provider within their Local or Wide Area Network (LAN or WAN).
2. No choice for the timing of surgery. Such services would be based on clinical triaging criteria only. This may result in clinically acceptable longer waiting times for benign and no risk surgeries. Healthcare IT Systems will ensure the impartiality and fairness of the system.
3. No choice for the service setting. Beneficiaries would be eligible only for general ward beds for in-patient treatments at a hospital along a designated referral pathway.
4. Medicare surcharge to be paid by those who do not obtain private insurance Cover despite being in the "affordable" category.

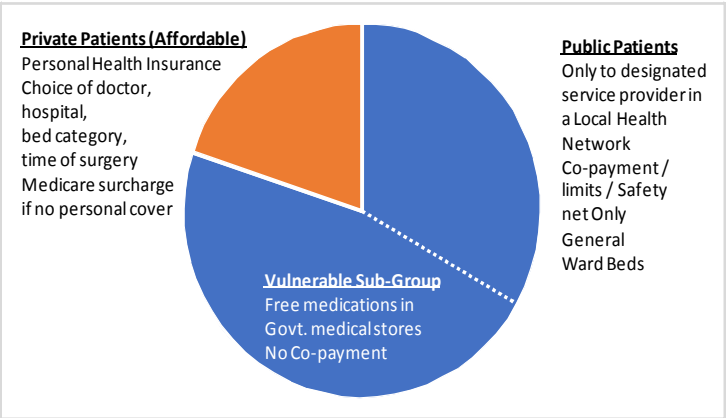

Fig 4 — Categorization of UHC Beneficiaries

Strategies for prevention of over-utilization :

User charges have been reported to negatively impact the very population that was being protected[9]. A meta-analysis of 255 studies explored the effectiveness of various strategies for controlling pharmaceutical expenditure in populations[10].The study supports influencing prescribers as the most effective strategy. The following strategies can be proposed:

1. Clinical Pathways or Protocols developed by the respective professional bodies for the commonest diseases. This will ensure that tests and medications are appropriately utilized and not over-utilized.
2. Co-payment of 20% for services to be paid by the "non-vulnerable" public patients. The vulnerable would be exempt from the co-pay.
3. Medications (Out-patient) without charges only from government medical stores and dispensaries.
4. Cap on the number of out-patient visits and the list of tests based on clinical effectiveness.
5. Generalists as gatekeepers to specialists and in-patient services have been an effective strategy in Canada, UK, and Australia.
6. Safety Net mechanism is an alternative model of the Universal Health Cover. People avail of the services that they need and are reimbursed fully for ongoing care after a pre-determined expenditure has been incurred. This prevents catastrophic expenditure.

Services to be funded – only those services and products that lead to a productive quality of life should be included in the UHC system.

Out-patient services by private facilities, including visits to doctors and diagnostics, is a vital component of the proposed Universal Health Cover system. Without adequate out-patient care, treatments of minor conditions will escalate to major conditions and will drive up the demand for much more expensive in-patient treatment.The out-patient services would be free for the vulnerable population group (40%) identified in the PM-ABJIYA scheme and the rest (40%) would pay for their own medications as well as a 20% co-pay for the tests and doctor's fees.

Response to Pandemics – the proposed model organizes the entire healthcare services into manageable units based on pin codes and legislative assemblies. It also brings the private service providers into the ambit of policies of the Government. Hence, healthcare service delivery responses to future pandemics and other disasters can be better coordinated by the government.

The Health Departments would be able to track index patients and outbreaks by pin codes, thereby, coordinating the supplies and logistics in a much better-informed process.

Governance and Payment System : A Council of Health Ministers is proposed based on the successful GST Council. This Council will be the empowered body to make national policies requiring minimum standards across the country. An amalgamation of the multitude of current agencies would provide for a more efficient system and cost savings to fund the Universal Health System.

Medicare India, Independent Health Pricing Authority, Local Area Health Networks, NABH, NABL, and other autonomous Government Agencies would implement the Universal Health Cover as well as improve governance. The Independent Health Authority is envisaged to set the index price for health services with public and private provider representation. The Authority will need to include experts from finance and actuarial sciences. Similar Authorities at the state level would apply modification factors on the national index price based on local costs. Medicare India is envisaged to maintain the register of service providers and service recipients with the allotment of respective identifier numbers. An important function would be to detect misuse and impose penalties.

There is a real urgent need to change the payment system in India from a Retrospective System to Prospective System based on defined "clinical products". DRG system has been successful in defining a clinical product and is based on the recognition that diseases can be arranged into groups that require similar resources to treat. Hence, the cost of treatment for diseases within a group will be the same. The DRG system was developed in the 1970s at Yale University and subsequently adopted by Medicare USA, Canada, UK, and Australia. It is also supported by WHO for implementation across the world and is being actively implemented in all European countries[2]. The purchase cost for any DRG can be arrived at by multiplying its weighted index and the index pricing (affixed by IHPA). Factors for geographical differences as well as incentives for education and clinical outcomes can be applied. A Prospective Payment System (PPS) based on Diagnostic Related Groups (DRG) will be the backbone for rationalizing costs and creating the sustainability of the system.

Healthcare IT will be an enabler of implementation, prevention, and detection of misuse. There are many DRG Grouper software available that automatically generate and report DRG based on the entry of ICD-10 codes. Use of e-cards, learnings from RSBY and other schemes as well as the deployment of a cloud-based electronic medical record (EMR) in private clinics and public facilities will lead to the implementation of a prospective payment system as well as the collection of vital health data for improving policy formulation (Fig 5).

Projected Additional Financial Requirement :

The data for arriving at assumptions on costs and frequency of healthcare have been based on the 75th Round of NSS Report[7]. Following rationales and assumptions have been applied :

1. Categories of the population: Private Patients 20%, Public (Non-vulnerable) 32%, and Public (Vulnerable) 48% of the population.
2. A Co-payment of 20% of the charges is accounted from the "Non-vulnerable" group.
3. Public and private facility usage patterns for both out-patient and in-patient services in both rural and urban areas have been used[7].
4. Only the cost of services in private facilities has been calculated as the services in public facilities are already being provided free of cost and are being funded by the Government through existing budgets.
5. Cost of Out-patient cover in private facilities– Rs. 11,369 crores

(a) The number of persons ailing within 15 days

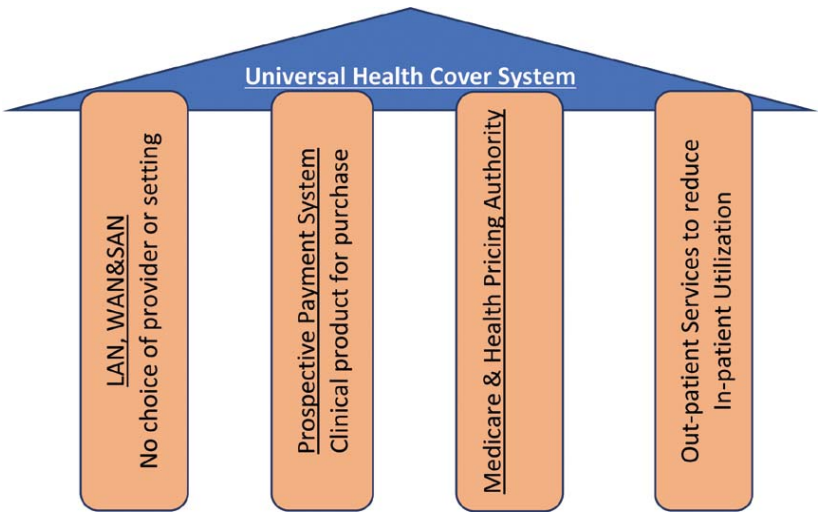

Fig 5 — Proposed Model of UHC in India

(based on PPRA) in India is 9 crores of which 5.6 crores are in rural and 3.4 crores in urban India[7].

(b) Of both groups, 45% have acute conditions, and 55% have non-communicable diseases[11,12]. One visit for Acute diseases and 0.17 visit for chronic diseases within the same 15-day period have been used for calculations.

(c) Data has been extrapolated for 365 days.

6. Cost of In-patient coverin private facilities– Rs. 28,896 crores

(a) The number of hospitalizations per year in rural India is 1.73 crores of which 54% avail private facilities. Of these, 56 lakhs are from the vulnerable group and 37.42 lakhs from the non-vulnerable group who pay a co-payment.

(b) Of the 1 crore beneficiaries in urban areas, 40 lakhs are the vulnerable and 26.6 lakh are the non-vulnerable availing private facilities (65%).

(c) Case-mix accounting has been done by calculating the numbers of each category for each disease system and the cost of private treatment for that disease system.

7. Total cost for Universal Health Cover (Medicare India) – Rs. 40,265 crores

(a) Out-patient Doctors fees – Rs. 7,200 crores

(b) Out-patient Diagnostic tests fees – Rs. 4,169 crores

(c) Private hospitals – Rs. 28,896 crores

Conclusion

In conclusion, Universal Health Cover is possible in India but success will require major healthcare reform in:

1. Inclusion of Out-patient services by private practitioners as a strategy for sustainability as well as for achieving public health care targets

2. Service delivery through both public facilities and private practitioners, organized into Local Area Networks based on residential pin codes

3. Clinical and Corporate Governance of the Local Area Networks through Wide Area Networks based on Legislative Assemblies

4. Creation of a Council of Health Ministers on the lines of the GST Council, Medicare India, and an IndependentHealth Pricing Authority

5. Changing healthcare reimbursements to a Prospective Payment System based on the DRG system

6. Computer software to drive the equitable distribution of referrals to specialists and hospitals.

Funding : None

Conflict of Interest : None

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Voice of the Experts

Following answers are given, singly or in collaboration, by following medicolegal experts.....

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Chairman, IMA HQs. Standing Committee For Legal Cell

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Chairperson, IMA MS Medicolegal Cell

(1) It is often seen that a section 304 IPC is registered against doctors after the death of a patient due to any reason. Can patient's relatives bring this murder charge at any time ? What should a doctor do in such cases ?

Yes, it's a fact. And a disheartened relative will try to influence the police to put the harshest section. In this connection, the doctor should take help of colleagues, Medicolegal consultant and local IMA or such organisation and go to the higher police authorities with famous landmark judgment Jacob Mathews v State of Punjab (Supreme Court Aug. 2005) and Dr Martin D'Souza v Mohd. Isfaq (SC 2009) which clearly mandates not to apply 304 but 304A only; and that too in exceptional circumstances. The latter decision goes one step further, warning police that SC will take suo moto action if this principle is violated. By giving a copy of these judgments, at least 5 times, such application was avoided, 3 times in Pune, once in Chandigarh and once in Bhuj. We had supplied this advice from IMA Pune. In 1 case in 2017, 6 doctors arrested had to be freed immediately once this position was clearly brought to the notice of Pune Police Commissioner.

In some states, doctors feel it safer to insist on registering any criminal complaint against them or the Health care establishment in case of a death under CrPC 174(3)(iv) citing doubt regarding cause of death.

(2) Sometimes, there have been cases when a doctor has been accused of sexual molestation while examining a female patient. What precautions can a doctor take to avoid such incidents ?

Precautions to be taken by a male doctor while examining a female patient :-

(a) Inform the female patient as to which private parts the male doctor will examine and why it is necessary. The patient should be convinced and expressly allow the examination.

(b) Examine any female patient in the presence of another female. May she be your staff (preferably), her relative or relative of another patient. If there is no other female present, don't examine the patient unless it is an emergency. In such cases, ensure that your staff and other males accompanying the patient are around.

(c) CCTV Camera is not allowed in the examination area. But, keep the adjacent area under surveillance of CCTV so that in case the patient behaves with an intention to falsely blame you, you can immediately move to the adjacent area under surveillance.

(4) If a female patient is below the age of 18 years, avoid examining. If because of unavailability of a female doctor and certain compelling circumstances e.g. required by law, a male doctor has to examine, please take consent of a female guardian of the child and follow above directions.

(3) Is there any Indian law regarding writing of death certificates? If a doctor sees a patient for the first time on his/her deathbed, should he write the certificate of death ? What should a doctor do if the patient party and local goons force him to write a death certificate ?

Yes, there is The Registration of Births and Deaths Act, 1969 which governs issuing 'Medical Certificate of Cause of Death'. Death certificate proper is issued by local authorities on the basis of the cause of death certificate issued by the doctor.

If a doctor sees a patient for the first time on his/her deathbed, he shall not write the certificate of death.

If the patient party and local goons force a doctor to write a death certificate, he shall politely counsel the related people as to why he can't issue the cause of death certificate, the legal bindings, etc. He should take help of the local IMA branch and medico legal experts while talking with these people. If still they force, he should inform the police.

(4) It is often seen that doctors are denied entry in their homes during this current pandemic. In some cases neighbours are forcing doctors to leave homes. What should a doctor do in such cases ?

Take help of police with the GRs (Government Resolutions) from various State Governments that prohibit such illegal behaviour from Society secretary, chairman or public. By force of law only, such a problem can be solved.

The state and central govt has announced that any personal preventing or objecting or even troubling in terms for rent payment to the frontline worker be it healthcare or others would be penalized under the Epidemic act.

If, in case, any person faces such a problem he should be well aware of such law and first try to convince the local society people that such law exists and convince them. Even in spite of this there is an objection he/ she has to bring it to the notice of local authorities and take necessary action.

It might so happen that even the local authorities are unaware of such a law or provision to help the frontline workers in a pandemic, so in such a situation he/ she has to educate the local authorities also, or it can be brought out through local IMA.

Be friendly with society and also be well read about the law which will always protect you.

(5) Suppose a doctor finds that some imposter is using his registration number to give out fake prescriptions of dangerous drugs. What should the doctor do in such cases ?

Always complain to the police with a copy to the commissioner of police of the region in writing and insist for acknowledgement. Send an email to the police commissioner also. Also mention in the application that I am not responsible for any consequences of the prescription as I disown the prescription totally. Attach Xerox copy of your registration. Send a copy of the same to the Medical council where you are registered.

(6) If a patient with an assault or street accident comes to a doctor in a private chamber and asks for a medical certificate of injury, can a doctor give such a legal document ? Or should the patient be sent to a government hospital ?

If the doctor (RMP) has treated the patient even as first aid or as emergency, he is legally authorised to give a certificate of injury. But doctors, many times, shirk away as he may be called by courts for testimony later on. (In short, to issue such an injury certificate is not 'cost effective') and therefore, the patient is asked to get treatment and certificate from a government facility.— This is practical.

All Private doctors are legally bound to treat an emergency patient and then if necessary refer them to higher center. Once they treat them they will be witnesses for the first hand information to the injuries.

These injuries should be documented and police intimation given. MLC registered.

Once this is done even if the case is referred to a higher center, the court or police will approach the primary treating doctor to give an injury certificate. While issuing this certificate one can demand the treatment received in the referred hospital to know the investigation done and treatment received before issuing a medical injury certificate.

(a) The doctor has to issue a medical injury certificate (in prescribed format) when demanded by the appropriate authority either police or court, not directly to the patient.

(b) Patient can just receive only a medical certificate to join back duty and so on and not the legal document.

(7) If a doctor sees a road traffic accident on the way and he cares for the victim, can he later be called to give evidence in court? Can a doctor be charged with negligence regarding treatment of such emergency cases ?

Yes, doctors can be called as a witness.

Also, if he gives treatment, he can be sued for negligence—however, as an expert medicolegal person, the doctor can definitely strongly argue that there was no established doctor patient relationship, as this DP relation was forced on him due to obiter dicta by Supreme Court (1989) in Parmanand Katara case. In fact there is such a case from the New Delhi State Consumer forum and the Pediatrician was penalised, but he should have gone in appeal on the above defense points.

Doctor when he cares for a accident victim on road is a general public with some expertise of medical knowledge without any material to treat except a first aid kit if he has. So as per The Supreme Court direction and approval of the Centre issued necessary guidelines with regard to the protection of Good Samaritans, no person who helps a victim of road traffic accident will be forced to reveal his identity nor will be forced by the police to come as a witness or evidence to court. Same applies to doctors also.

But if the doctor takes him to his hospital make a document on this patient and treats him in the hospital premises, then he will be called for evidence and also can be booked for any type of negligence.

Any act done in good faith and to help the patient live his life will be upheld in the court of law with proper documentation.

(8) If a patient party alleges that the degree of a doctor is false and complains in the police station, can the OC of the station demand to see the certificate of the doctor? Such incidents have happened.

Police have no authority to ask for the degree certificate to verify the document, as they have no expertise to check it. Instead the OC duty is to raise a query with concerned district health officer or the Medical council to verify them. If in case they demand the certificate for verification it is the duty of the doctor to produce the same.

Display all necessary documents like degree certificate, medical council registration certificate and all major licenses of the hospital or clinic in a visible place. In in the present era of smartphones they can take a pic of it and get it verified. If we are truthful we need not worry. But can easily avoid harassment by the police.

(9) If a consumer court awards a compensation amount to a patient party, which is greater than the lifetime income of a doctor, what should a doctor do ? Is he/she bound to pay the compensation amount selling all his properties ?

The oretically, yes, he will have to pay (jokingly, sell himself and pay!!).

If a consumer court awards a compensation amount to a complainant which is more than the total liquid money available with the doctor. The complainant can file a recovery suit to execute the court decree in the civil court of the jurisdiction where the doctor resides, practices or holds the property .

By going through Order 21 rule 30 of C.P.C, every decree for the payment of money, including a decree for the payment of money as the alternative to some other relief, may be executed by detention in the Civil Prison of the judgment debtor or, by the attachment and sale of his property, or by both.

According to Order 21 rule 31(1) of C.P.C, when the decree is for any specific movable property, the execution can take place in any of the following made:

- By seizure and delivery of the property.
- By detention of the judgement debtor (here is the doctor)
- By attachment of his property.
- By attachment and detention both.

According to Order 21 rule 35 sub-rule-1 of C.P.C, A court executing a decree has the power to attach the property and sell the property or portion thereof which is sufficient to satisfy the decree. After such attachment the first step is issuing a proclamation of sale. Such a proclamation shall be prepared after notice to both the sides and shall comprise of following details: -

- Time and place of sale.
- Details of property or part thereof to be sold.
- Revenue if any attached to property.
- Encumbrance to which the property is liable.
- Amount to be recovered under the decree.
- Such other particulars which the court considers material.

Better to — 1. Defend well. 2. Appeal against disproportionately high compensations 3. Have huge indemnity insurance coverage 4. Join IMA PPS

(10) It is now seen that in India, courts often reward patient parties with hefty compensation amounts. What is the basis for calculation of such compensation claim ?

Previously, and even now, majorly it is on the basis of compensation described in motor vehicle accident cases. However, in the Kunal Saha vs Amri Hospital, Dr Sukumar Mukharjee case in 2013 (Supreme Court), courts have adopted different calculations—"Quantum of Damages" for pain + expected income in lifetime of the applicant with increments + loss of companionship + pain + actual expenses + mental suffering. –it came to 6.5 Cr + 5.5 Cr as interest @ 6%. Of course that case is in appeal (as we know the position as of today) in full bench of SC.

Again, the principles remain the same, see answer to Q.9 above.

(11) How long should a doctor preserve patient data for future possible medicolegal cases? In India, where doctors often operate independently without any institutional support, how should a doctor preserve such data ?

MCI says, preserve indoor paper for 5 years, we suggest, preserve for 7 years.

Courts usually follow the UK system, which says, 6 years—so 7 years is a good period.

OPD papers, 3 years (MCI does not specify)

All Medicolegal (accident, suicide, poisoning, OT death, police registered or criminal case, etc)—preserve for 30 years (or better, till doctor dies!!)

For children and Obstetric cases, till the baby becomes 21 years.

For MTP, Tubectomy, PCPNDT—2 years

For Mentally retarded patients forever till the person is practicing.

Whenever, you receive a notice, or court intimation, always preserve till our life time!

<u>Period of limitation</u>—

Consumer case—2 years

Civil court—3 years

Criminal case—No time limit

Human rights—no time limit

However, there is a lot of discretionary power to the judiciary to condone delay and hence, let's stick to the regimen mentioned above.

Hence, to be much safer **all cases papers should be preserved lifelong.**

Doctors can have paper records, authentic electronic records, microfilming etc.

(12) In cases like coronavirus pandemic, where there is threat to life, can a doctor be forced by the government or private sector to work in covid ward? Is there any way a doctor can legally avoid such dangerous duties ?

Yes, the government can force covid duties. Take help of govt./ICMR guidelines to say no for such duties, like age>55-60, diabetes, hypertension, nephropathy etc. Take help of Medicolegal expert. They can help legally to avoid such duties legitimately. Also check if the government is giving insurance cover, PPE, etc. as directed by the Supreme Court.

It is the government duty to protect the lives of the people following the orders by giving them adequate protection and reasonable remuneration.

(13) If a doctor gets beaten up by the patient party and there is long term illness due to assault, can the doctor claim compensation from the party? What are the mandatory evidence a doctor should preserve for such cases?

Doctor being a citizen of the country first and then a doctor, any assault by anyone he is entitled to claim compensation for any type of injury either small or long term. The evidence of assault if any like videos and eye witness of the incident should be preserved including that written in the case sheet of the patient that such an incident has been created in the hospital premises.

Fighting out and booking a case after the assault by the lawyer of the doctor is very essential to claim for compensation.

(14) If a newspaper publishes a false report on "negligence" of a doctor without proof, can a doctor go to court ? What about false news on TV ?

Yes, you can go against the media—(TV included). You can put your grievance to the press council of India, Information and Broadcast ministry, police case

for falsified information, criminal intimidation, criminal defamation; and in civil side, put a huge claim of defamation. Also take help of your professional association, which ought to be strong and fighter, medicolegal experts, lawyers, who will guide, support and raise even funds to get injustice removed and the offender being punished.

The doctor has to send a legal notice to the chief editor or the media channel stating that by this false news, he has faced significant defamation and also financial losses. Following which if there isn't any an appropriate reply for them the doctor can file a criminal defamation case against the media cell.

Keep good rapport with local media and if any such false news is published see it to it that you try to give an appropriate factual clarification. If still it continues to defame you, file a criminal defamation case.

Thank you Dr TN Ravisankar, Dr Jayant Navarange, Dr Dinesh Thakare, Dr Pavankumar Patil and Dr Ashok Shukla, ***for giving the invaluable insight regarding the medicolegal issues regularly faced by doctors.***

Original Article

Comparative study between saline infusion sonohysterography and diagnostic hysteroscopy in diagnosing endometrial pathology in patients of abnormal uterine bleeding

Pranab Kumar Biswas[1], Sushanta Kumar Pain[2], Sandhya Das[2], Fakra Masroor[3], Sohini Munshi[4], Manoshi Santra[4], Soumen Patra[4]

Background : Abnormal Uterine Bleeding (AUB) is a common but complicated clinical presentation, diagnosis of which is often difficult. The cause may be variable of which endometrial pathology is an important component. Saline infusion sonohysterography (SIS) is a procedure in which a transvaginal scan is done after instilling normal saline into the uterine cavity, thus providing a better visualisation of endometrial cavity.

Objective : This study was aimed at the comparison of the diagnostic accuracy of SIS for each of the individual endometrial pathologies (endometrial polyps,endometrial hyperplasia and submucous fibroids) taking versus hysteroscopic findings, accepting hysteroscopic assessment as the gold standard. Precisely, Positive predictive values Sensitivity, specificity, and negative predictive values of SIS were evaluated here.

Material and Method : The study was performed inDepartment of Gynaecology and Obstetrics, Calcutta National Medical College and Hospital on 50 cases for a period of 1 year (June 2015-May 2016). Cases of AUB with suspected endometrial pathology diagnosed in GOPD clinically and by commonly available diagnostic tools(USG, blood parameters etc.) were included. The sensitivity (SN), specificity (SP), positive (PPV) and negative predictive value(NPV) for polyps were 83.3, 92.1,76.9 and 94.6 respectively. For submucous fibroids SN, SP, PPV and NPV were respectively 84.6, 97.3, 91.2, 94.7. Endometrial hyperplasia detection showed similar values (SN=73.3, SP=97.1, PPV=91.7, NPV=89.7).

Conclusion : The study concluded that,compared to hysteroscopy SIS is cost effective.The sensivity and specificity of SIS are comparable to hysteroscopy in evaluating endometrial pathology. Its use as a pre-operative evaluation shows promise as it may help avoid major surgical interventions and its associated morbidities.

[*J Indian Med Assoc* 2020; **118(9):** 31-5]

Key words **: Saline Infusion Sonography (SIS), Trans-vaginal Sonography(TVS), Hysteroscopy, Sabmucous fibroids, Polyps, Endometrial hyperplasia.**

AUB or Abnormal Uterine Bleeding is a common but complicated clinical presentation, diagnosis of which is often difficult as the cause may be variable from simple Dysfunctional Uterine Bleeding to endometrial carcinoma. AUB is said to occur in 9-14% women between menarche and menopause[1]. The prevalence varies in each country. In India the reported prevalence of AUB is around 17. Frequently, patients with Abnormal Uterine Bleeding undergo a transvaginal scan followed by diagnostic or therapeutic hysteroscopy. These approaches rarely evaluate the endometrial components and hence falsely stamp

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Received on : 11/10/2017
Accepted on : 08/09/2020

Editor's Comment :

- **AUB is a very common presentation in Gynecology OPD.**
- **Diagnosis of AUB is often difficult with available diagnostic procedures.**
- **Endometrial pathology (like polyp, submucous fibroid, hyperplasia etc) needs MRI or Hysteroscopic evaluation.**
- **Hysteroscopy is considered as gold standard in diagnosing endometrial pathology but it is costly and there is procedure related complications.**
- **MRI is costly and not readily available everywhere.**
- **SIS is simple,affordable, without any major procedural complications, and is comparable in Sensitivity, Specificity, Positive and Negative predictive values with Hysteroscopy in diagnosing endometrial pathology.**

them as DUB (ie, bleeding in absence of any pelvic pathology. Sonosalpingography (SIS) is a modified transvaginal scan wherein scanning is done during infusion of normal saline into uterine cavity to diagnose endometrial pathologies. The study was done to see if saline infusion sonohysterography could compare with hysteroscopy for the diagnosis of endometrial pathology in patients with menstrual abnormalities. SIS and hysteroscopic findings of endometrial polyps, submucousmyomas, endometrial hyperplasia etc.were recorded and subsequently compared.

Terminologies:

Any deviation from normal parameter was treated as abnormal in our study. In order to define normal menstrual bleeding we took the following guideline as our reference.

Suggested terminologies for normal Menstrual Parameters in the Mid-Reproductive Years[3] (Fig 1).

Usual Menstrual cycle parameters	Descriptive terms	Normal limits (5^{th}-95^{th} percentile)
Interval between menstruation	Normal	24-38 days
Variation of menstruation over 12 months	Regular	Variation 2-20 d
Number of days the flow happens	Normal	4.5-8 days
Amount of blood loss (ml)	Normal	5-80ml

Causes of A.U.B (FIGO classification)

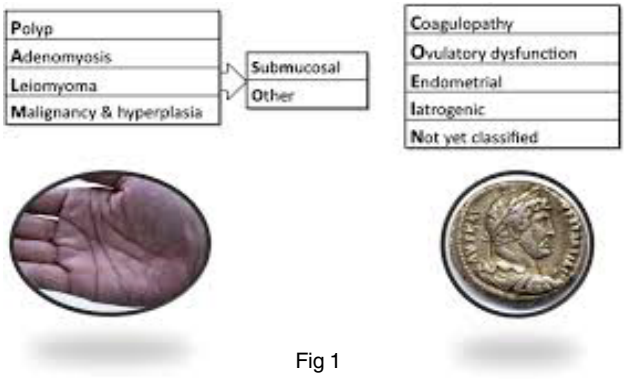

Fig 1

Materials And Methods

STUDY LOCATION : Department of Obstetrics and Gynaecology and Department of Radiology of Calcutta National Medical College and Hospital.

STUDY POPULATION : Women admitted in OBGYN dept. with Abnormal Menstruation.

STUDY PERIOD : One year (June 2015-May 2016)

SAMPLE SIZE : 50 (fifty) cases.

SAMPLE DESIGN : Those patients who attended Outpatient Department in Obstetrics and Gynaecology department with Abnormal Uterine Bleeding were examined clinically and selected for SIS and Diagnostic Hysteroscopy

INCLUSION CRITERIA : AUB (as defined by bleeding not following the normal menstrual parameters) with suspected endometrial pathology diagnosed in GOPD clinically and by commonly available diagnostic and ancillary aids

EXCLUSION CRITERIA : 1. Pregnancy 2. Virgin women 3. Pelvic inflammatory disease 4. Morbid medical illness 5. Any diagnosed cause of menstrual abnormality by clinical or diagnostic aids. 6. Patients whose uterine cavity could not be distended by saline infusion or SIS could not be performed due to other causes.

STUDY DESIGN : Prospective comparative study for assessing the efficacy of Saline Sonography in diagnosing uterine cavity abnormalities in comparison with hysteroscopy.

PARAMETERS STUDIED : Endometrial thickness, uterine cavity contour, polyps and synechaie seen by SIS along with Hysteroscopic findings of uterine cavity including polyps, endometrium, etc.

STUDY TOOLS : **(1) Saline infusion sonohysterography :** TVS probe, standard HD7 philips mode USG machine, SIS cannula (polyethylene, 26cm with acorn shaped guard), vaginal speculum and other minor aids for cleaning and draping , analgesics. **(2) Hysteroscopy :** A 30 degrees rigid hysteroscope was used with a telescope of 4mm outer diameter. The outer sheath had an outer diameter of 8 mm, and contained ports for instillation of the distending medium. An obturator fitting the outer sheath was also provided to simulate a smooth, blunt dilator.

STUDY TECHNIQUE : Those patients who attended GOPD with clinically undiagnosed A.U.B. were asked to participate voluntarily after explaining the purpose of the study and consent taken. Relevant history was taken from such patients regarding age, weight, parity, menstrual history, family history, surgical history. A brief pelvic examination was done and investigations reviewed. Patients were selected for the study matching the inclusion and exclusion criteria. Such patients were then examined by saline infusion sonohysterography. Observations such as endometrial hyperplasia, polyps, synechiae, submucous myomas as well as normal findings were recorded. The same patients were kept for diagnostic hysteroscopy under general anaesthesia. The findings of SIS were compared with hysteroscopic findings set as gold standard.

SIS Technique:

Timing : As soon as possible day 6 to day 11 -

during proliferative phase of menstrual cycle (regular cycle) after stoppage of bleeding. In cases of irregular cycles, it was done after the bleeding was controlled.

Patient preparation : Oral NSAIDS were given 1 hour before examination and a Routine TVS for pelvic assessment was done.Patient was placed in lithotomy position after a Brief bimanual examination**.**

Procedure : Sterile speculum was placed in vagina and cervix brought into view.Catheter was placed at internal os and advanced through stiffener into the endometrial canal.Speculum was gently withdrawn and Trans-vaginal probe inserted beside catheter.5-30 ml of normal saline injected and 2d imaging was done in both sagittal and coronal sections. 3D imaging and doppler were done to differentiate blood clots from polypoid lesions. The patients were seen to tolerate the procedure well.

Diagnostic Hysteroscopy Technique :

A diagnostic hysteroscopy was performed subsequently in such subjects and uterine cavity was analysed thoroughly.

Analysis of Data :

The data collected was tabulated, compared and analysed by standard statistical methods in consultation with statistician, department of community medicine. Inferential analysis as performed using the chi-square test. Cohen's kappa coefficient was used to measures inter-rater agreement for qualitative items.

Discussion

Saline infusion sonohysterography has its own advantages. Apart from being associated with very minimal complications, it is cost effective, easy to perform and well tolerated by most patients. Thus, the American College of Radiology, the American Institute of Ultrasound in Medicine and The American College of Obstetricians and Gynecologists has developed a technology assessment document for saline sonography.

Indications of SIS include Post menopausal bleeding, endometrial polyps, Leiomyomata, endometrial hyperplasia / carcinoma,Tamoxifen therapy, Mullerian anomalies, masses and intra uterine adhesions, recurrent pregnancy loss etc.

Contraindications of SIS are Pregnancy, active Genital tract bleeding or acute genital infections.

SIS helps to presumptively diagnose the endometrial causes of AUB. Thus, it helps to select candidates for endometrial sampling. It gives a fair idea about candidates who needs a focal lesion to be sampled versus candidates who can be taken up for opd pased pipelle sampling.

Hysteroscopy is the inspection of the uterine cavity by endoscopy with access through the cervix. Besides diagnosing intrauterine pathologies, operative hysteroscopy may help in correcting such pathologies. Hysteroscopy is useful in diagnosing a number of uterine conditions:[4]

- Asherman's syndrome (i.e. intrauterine adhesions).
- Endometrial polyp.
- Gynecologic bleeding (submucous fibroids, endometrial hyperplasia)
- Congenital uterine malformations (also known as Mullerian malformations).

Apart fom these, hysteroscopy has some definite therapeutic advantages like performance of polypectomy, endometrial ablations, submucous myomectomy etc which is beyond the scope of this study.

The use of hysteroscopy in endometrial cancer is not established[5] as there is concern that cancer cells could be spread into the peritoneal cavity. Compared to blind procedures performed on delicate reproductive tissues of uterus, hysteroscopy performed under visualisation reduces iatrogenic trauma to a large extent.

Results

SIS * HYSTEROSCOPY Crosstabulation

		HYSTEROSCOPY				Total SIS
		A	B	C	D	
SIS	A	10	0	0	3	13
	B	0	11	1	0	12
	C	0	1	11	1	13
	D	2	1	3	6	12
Total Hyst.		12	13	15	10	50

A=polyp, B=submucous fibroid, C=endometrial hyperplasia, D=normal findings

Polyps

SIS	HYST		TOTAL
	YES	NO	
YES	10	3	13
NO	2	35	37
TOTAL	12	38	50

Sensitivity	Specificity	Positive predictive value	Negative predictive value	Percentage agreement
83.3	92.1	76.9	94.6	90

From the above chart, it is clear that though SIS is highly sensitive for detection of polyp, it is more specific (92.1) than sensitive (83.3) in this regard

Submucous fibroids			
SIS	HYST		TOTAL
	YES	NO	
YES	11	1	12
NO	2	36	38
TOTAL	13	37	50

Sensitivity	Specificity	Positive predictive value	Negative predictive value	Percentage agreement
84.6	97.3	91.2	94.7	94

For submucous fibroids, sensitivity(84.6) is almost equivalent to polyp detection, but here again specificity (97.3) is more than sensitivity leading to a higher negative predictive value.

Endometrial hyperplasia			
SIS	HYST		TOTAL
	YES	NO	
YES	11	1	12
NO	4	34	38
TOTAL	15	35	50

Sensitivity	Specificity	Positive predictive value	Negative predictive value	Percentage agreement
73.33	97.14	91.7	89.7	90

Coming to endometrial hyperplasia detection, my study has shown a good sensitivity (73.3), but it is low compared to polyp and submucous fibroid detection. But here positive predictive value has been observed to be greater than negative predictive values when compared with polyps and fibroids.

Test Statistics			
SIS			
	Observed N	Expected N	Residual
A	13	12.5	0.5
B	12	12.5	-0.5
C	13	12.5	0.5
D	12	12.5	-0.5
Total	50		
HYSTEROSCOPY			
	Observed N	Expected N	Residual
A	12	12.5	-.5
B	13	12.5	.5
C	16	12.5	3.5
D	9	12.5	-3.5
Total	50		

Significance		
	SONOHYS	HYSTERO
Chi-Square	0.080[a]	2.000[a]
df	3	3
Asymp. Sig.	0.994	0.572

[a]0 cells have expected frequencies less than 5. The minimum expected cell frequency is 12.5.

Symmetric Measures				
	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	0.680	0.080	8.337	0.000
N of Valid Cases	50			

[a]Not assuming the null hypothesis.
[b]Using the asymptotic standard error assuming the null hypothesis.

Saline sonography performed well in our study was comparable to diagnostic hysteroscopy[6,7]. It's sensitivity in detecting polyps, submucous fibroids and endometrial hyperplasia was 83.3%, 84.6% and 73.3% respectively. Its specificity as found in our study for the detection of the above pathologies in the same order were 92.1%, 97.3% and 97.1% respectively. Apart from these, the predictive values found in our study (both positive and negative) and that done by bingo et al in 2011[6] were comparable. The level of significance as determined by chi square tables were 0.08 for SIS and 2.00 for hysteroscopy (degrees of freedom-3) indicating the increased probability of erroneous findings being accepted as true. But, such findings are a result of a small sample size with increased number of variables observed in the study.

Undiagnosed AUB constitutes a large burden to gynaecological OPD in all hospitals.The socio demographic characteristics of such undiagnosed abnormal uterine bleeding has a variable pattern Some of these undiagnosed cases are often stamped as dysfunctional uterine bleeding without assessing endometrial pathology. In our study, we established that endometrial pathologies like polyps and submucous fibroids constituted a major bulk of AUB often missed by common investigative tools. SIS proved to be an efficient process by which intrauterine pathologies were identified with ease. Compared to hysteroscopy it is cost effective, involves minimal aids and has lesser inter observer variability. It has some minor technical difficulties like stenosed internal os which may lead to inability to pass catheter or blood clots which may mimic polyp. The sensivity and specificity of Saline infusion Sonohysterography are comparable to hysteroscopy in evaluating uterine cavity as demonstrated by our study and corroborated by other studies. Whereas hysteroscopy is still considered a costly investigation owing to its requirement of a hysteroscope and anaesthetic procedures, SIS is more cost effective and with lesser complications. Its use as a pre operative evaluation shows promise as it may help avoid major surgical interventions and its associated morbidities resulting

in better utilisation of hospital resources.

Funding : None

Conflict of Interest : None

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Original Article

Non-vitamin K Oral Anticoagulant prescription for stroke prevention in atrial fibrillation : Perceptions among physicians in a metropolis

Saumitra Ray[1], Suvro Banerjee[2]

Objective : To study the trend in use of the NOACs amongst the physicians and also to explore the reasons behind the choice of a particular NOAC.

Methods : An on- line survey was conducted amongst the physicians of a metropolis, based on an arbitrary case scenario

Results : Dabigatran was found to be preferred by majority of physicians. Inappropriate low dosing was more common with dabigatran and rivaroxaban. Of the Dabigatran brands, the original research brand was mostly preferred. Efficacy and safety were the predominantly cited reasons for preferring one NOAC over the others. Although not statistically significant, there were some differences in prescription habit for NOACs between the cardiologists and internists.

Conclusion : Dabigatran was the NOAC most preferred by the physicians practising in Kolkata. The reason for choosing one NOAC over the others was largely driven by perceived efficacy and safety, rather than cost or availability of an antidote.

[*J Indian Med Assoc* 2020; **118(9):** 36-40]

Key words **: Atrial fibrillation, Kolkata, NOAC, prescription preference, physicians, stroke, survey.**

Over the last decade, vitamin K antagonist (VKA) is being gradually replaced by non-VKA oral anticoagulant (NOAC) as the oral anticoagulant of choice in nonvalvular atrial fibrillation (NVAF). This trend is more obvious in the urban setting compared to rural, and in private sector compared to the government- run health sectors. The reason for this discrepancy is likely economical, as the NOACs are considerably more costly than VKA. The complexity of VKA use and the need for regular blood tests cannot fully overcome the financial constrains to the use of NOACs[1].

However, the introduction of generic dabigatran in the Indian market has changed the scenario. Many more people now can afford these cheaper generic drugs. On the other hand there are issues of compliance with a single daily dose of rivaroxaban versus the twice daily doses of dabigatran and apixaban. When prescribing, clinicians also consider the real or perceived side effects of NOACs such as higher incidence of myocardial infarction and gastrointestinal bleeding with dabigatran, and less thromboembolic protection with the lower dose of apixaban. The high prescription of lower doses of NOACs as compared to the doses used in the setting of the clinical trials with NOAC, is also an issue of concern.

Editor's Comment :

- **The survey brought out useful information on the practice of use of novel oral anticoagulants in atrial fibrillation by physicians practicing in and around Kolkata.**
- **It showed that of the four considerations to choose one NOAC over others, namely, efficacy, safety, cost and availability of antidotes, the first two were prime factors.**
- **Dabigatran was the NOAC of choice as revealed in this survey.**
- **Original brand molecule was still preferred over cheaper generic versions.**

We conducted a survey in the metropolitan city of Kolkata to find out the trend in use of the NOACs amongst the internists, Cardiologists and Neurologists and also to explore the reasons behind the choice of a particular NOAC.

Materials and Methods

Survey Questionnaire :

A short and simple survey was designed to test physicians' perception and mindset regarding prescription of NOACs [Fig1]. The survey consisted of three questions set in reference to a given clinical

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Received on : 31/01/2020

Accepted on : 01/07/2020

A 69 year old man with hypertension and diabetes presents with AF. No other comorbidity. No history of bleeding. He is on Telmisartan and Metformin. Renal and liver functions are normal. CHA_2DS_2VaSc score 3, HAS-BLED score 2.

Q1. Which of the following NOACS will you choose and at what dosage?

- Dabigatran 150 mg BD
- Dabigatran 110 mg BD
- Apixaban 5 mg BD
- Apixaban 2.5 mg BD
- Rivaroxaban 20 mg OD
- Rivaroxaban 15 mg OD
- Generic Dabigatran 150 mg BD
- Generic Dabigatran 110 mg BD

Q2. What is the most important reason for your choice?

- Effectiveness
- Safety
- Compliance
- Cost

Q3. What describes you best?

- Cardiologist
- Neurologist
- Internist

Fig 1 — Clinical scenario and the survey questionnaire

scenario. The first question was designed to test which of the three available NOACs (apixaban, dabigatran or rivaroxaban) would be of choice to a physician in a clinical situation where any of the three NOACs could be used. Dabigatran was further divided into the branded and the generic types that were available. For each NOAC, there was the option to use the higher or the lower dose. The second question was about the reason for the choice. The third question was to determine whether the physician was a cardiologist, neurologist or internist. Only one answer was allowed for each question stem and the participant was required to choose the answer from a drop-down menu.

Subjects :

Requests for survey were sent to 150 physicians who are practicing in Kolkata. Physicians were chosen at random from the directories of the Cardiological Society of India and the Association of Physicians of India (seventy-five from each of the directories). Only Cardiologists, Neurologists and Internists (with MD qualification) were chosen for the survey.

Methodology :

The software 'Survey Monkey' was used to get the response from the participants. Only first 100 responses were planned to be considered as per the existing software capability. The survey was anonymous and was designed so that it cannot be taken more than once by a participant.

Analysis :

The result was further analysed by the software. The higher dose of the chosen NOAC was considered to be the appropriate dose in the given situation as there was no reason to prefer the lower dose. Chi-square test was used to assess statistical significance.

Results

Responders :

Of 150 surveys sent, 112 responded. The first 100 of the responses were considered. 18 responses were incomplete and therefore excluded from the study. Out of 82 respondent physicians who were considered for the study, 45 (54.9%) were Cardiologist, 4 (4.9%) were Neurologist and 33 (40.2%) were Internists

Results, all Specialties Combined :

The choice and the dose of NOAC all specialty combined, is given in Table1. Of the 82 respondents, dabigatran was preferred by 58 (70.7%), apixaban 13 (15.9%) and rivaroxaban 11 (13.4%) [Fig 2]. This greater preference for dabigatran among physicians compared to apixaban and rivaroxaban was statistically significant ($p<0.00001$).

The higher dose of any NOAC (the appropriate dose in this case) was considered by 48 (58.5%) of 82 respondents. The inappropriate lower dose in this case was selected by 28 (48.3%) out of 58 of dabigatran prescribers, 1 (7.7%) of 13 apixaban prescribers and 5 (45.5%) of 11 rivaroxaban prescribers.

Of the 58 physicians preferring dabigatran, the generic dabigatran were considered only by 9 (15.5%) physicians.

The reasons for preference among all specialty

Table 1 — *Overall choice of NOAC and dosage (NOAC= Non-vitamin K oral anticoagulant)*

Dosage of NOAC	Number (n=82)	Percent
Dabigatran 150 mg twice daily	23	28.0
Dabigatran 110 mg twice daily	26	31.7
Apixaban 5 mg twice daily	12	14.6
Apixaban 2.5 mg twice daily	1	1.2
Rivaroxaban 20 mg once daily	6	7.3
Rivaroxaban 15 mg once daily	5	6.0
Generic Dabigatran 150 mg twice daily	7	8.5
Generic Dabigatran 110 mg twice daily	2	2.4

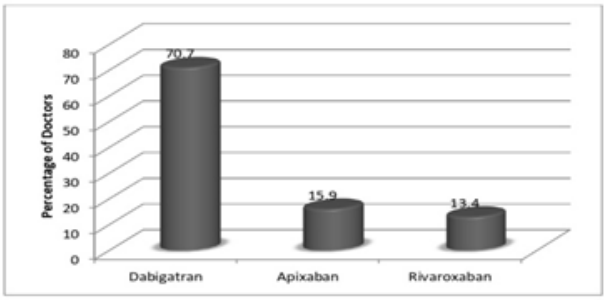

Fig 2 — Percentage of physicians of all specialties choosing a particular NOAC

combined, were cited as effectiveness by 28 (34.1%), safety 25 (30.5%), better compliance 10(12.2%), cost 10 (12.2%) and availability of antidote 9 (11%) [Table 2]. This difference between efficacy and safety on one hand and compliance, cost and antidote availability on the other hand, appeared statistically significant (p <0.00001).

Results Filtered as per the Specialties :

When the data were filtered as per the specialties, among the cardiologist [Table 3], (n=45), thirty-two (71.1%) opted for dabigatran, 5 (11.1%) for apixaban and 8 (17.8%) for rivaroxaban. Twenty-nine (64.4%) considered the appropriate dosage. Of the 32 who considered dabigatran, only 6 (18.8%) preferred generic dabigatran. The reason for preference was cited as effectiveness by 17 (37.8%), safety 10 (22.2%), better compliance 5(11.1%), cost 8 (17.8%) and availability of antidote 5 (11.1%).

Among the Internists [Table4](n=33), 24(72.7%) opted for dabigatran, 7 (21.2%) for apixaban and 2 (6.1%) for rivaroxaban. Fourteen (42.4%) considered the appropriate dosage. Of the 24 who considered dabigatran, 3 (12.5%) preferred generic dabigatran. The reason for preference was cited as effectiveness by 9 (27.3%), safety 15 (45.5%), compliance 4(12.1%), cost 2 (6.1%) and availability of antidote 3 (9.1%).

Among the Neurologist (n=4), 2(50%) opted for dabigatran, 1 (25%) for apixaban and 1 (25%) for rivaroxaban]. Three (75%) considered the appropriate dosage. Of the 2 who considered dabigatran, none preferred generic dabigatran. The reason for preference was cited as effectiveness by 2 (50%), safety 0 (0%), compliance 1(25%), cost 0 (0%) and availability of antidote 1 (25%).

Table 2 — *Most important reason for the choice of a particular Non-vitamin K oral anticoagulant*

	Number (n=82)	Percent
Effectiveness	28	34.1
Safety	25	30.5
Compliance	10	12.2
Cost	10	12.2
Availability of antidote	9	11

Table 3 — *Choice of NOAC and dosage among Cardiologists (NOAC= Non-vitamin K oral anticoagulant)*

Dosage of NOAC	Number (n=45)	Percent
Dabigatran 150 mg twice daily	15	33.3
Dabigatran 110 mg twice daily	11	24.4
Apixaban 5 mg twice daily	5	11.1
Apixaban 2.5 mg twice daily	0	0
Rivaroxaban 20 mg once daily	4	8.9
Rivaroxaban 15 mg once daily	4	8.9
Generic Dabigatran 150 mg twice daily	5	11.1
Generic Dabigatran 110 mg twice daily	1	2.2

Table 4 — *Choice of NOAC and dosage among Internists (NOAC= Non-vitamin K oral anticoagulant)*

Dosage of NOAC	Number (n=33)	Percent
Dabigatran 150 mg twice daily	7	21.2
Dabigatran 110 mg twice daily	14	42.4
Apixaban 5 mg twice daily	6	18.2
Apixaban 2.5 mg twice daily	1	3.0
Rivaroxaban 20 mg once daily	1	3.0
Rivaroxaban 15 mg once daily	1	3.0
Generic Dabigatran 150 mg twice daily	2	6.1
Generic Dabigatran 110 mg twice daily	1	3.0

Discussion

To the best of our knowledge this is the first survey of physicians' perception regarding NOAC prescription in Eastern India. Several interesting findings came out of our survey.

Firstly, dabigatran is the clear first choice by majority of clinicians. Dabigatran, both the branded and the generic versions together, was the choice of 70.7% of responders. Apixaban was chosen by 15.9% and rivaroxaban by 13.4%. At first thought it may appear that this preference for dabigatran is due to the availability of the cheaper generic version of dabigatran and that it is the only NOAC which has got an antidote. But the survey reveals a completely different story.

Of the 58 dabigatran prescribers, 84.5% preferred the more expensive branded molecule and only 15.5% opted for the cheaper generic version. Therefore cost was not prime consideration for the choice as branded drug prices were similar for all three NOACS. Cost was a consideration for only 12.2% of clinicians.

Also, the reason for the choice was not the availability of antidote (only 11%), but rather efficacy or safety. Why dabigatran scored over the other two NOACS in terms of safety or efficacy could not be explored by this survey as that was beyond the scope of our study, but this opens up an interesting aspect of physicians' prescribing habits and the factors that

influence such habits. Perhaps physicians' familiarity with dabigatran may be an important factor in their decision making process, as dabigatran has been available in the market few years ahead of the other two NOACs.

In the pioneering trials of the three NOACs, namely, RE-LY[2], ROCKET-AF[3] and ARISTOTLE[4], there was hardly any difference with the outcome when used in proper dosing. There was initial concern about dabigatran causing more acute myocardial infarction which was later refuted by large registry data mostly from the USA. Incidence of GI bleed is higher with dabigatran and rivaroxaban compared to apixaban[5]. Also, as dabigatran is extensively excreted via urine, its use is to be carefully monitored below creatinine clearanace (CrCl) of 50 ml/min and it is not recommended below of 30 ml/min. Rivaroxaban and apixaban, on the other hand, has less renal excretion and can safely be used upto CrCL 30 ml/min or even lower. Thus, there is no evidence to suggest that dabigatran is safer than the other NOACs.

It is perceived that rivaroxaban improves compliance because of its once daily dosing schedule. Across the speciality of medical practice, compliance is an important issue and there are enough data to show that compliance is inversely proportional to the number of pills. But in our survey, only 12.2% of clinicians considered this as an important issue for choice of a NOAC. One explanation may be that they were allowed to give only one response, and efficacy and side effects of drugs took priority over compliance in their decision making process. An all-choice option with relative scoring might have revealed the compliance issue as also an important co-factor while choosing a drug.

Another interesting observation was the difference of choice between the Cardiologists and the Internists. We do not consider the opinions of the Neurologists separately as they were only four out of a total of 82 prescribers. Though the trend is same in favour of dabigatran, the differences are also interesting. Of the Cardiologists, 71.1% chose Dabigatran, 11.1% apixaban and 17.8% rivaroxaban. For the internists the corresponding values were 72.7%, 21.2% and 6.1%. Although not statistically significant (p=0.19), more Cardiologists seem to prefer rivaroxaban over apixaban and the reverse is true for the internists. Also, among the physicians prescribing dabigatran, the generic version was more often chosen by the Cardiologists (18.8% of all dabigatran prescription by Cardiologists) compared to the Internists (12.5% of all dabigatran prescriptions). There is no obvious explanation for this. We did not explore the socioeconomic status (SES) of the patients that the clinicians see in their practice, though it is unlikely to be a big difference between the SES of patients seen by Cardiologists and the Internists.

The inappropriate use of the lower dose of a NOAC is a problem all over the world. Real world data[5,6] show that the use of lower dose (15mg) of rivaroxaban was 20.1% and that for apixaban (2.5 mg) was 26.9%. On the contrary, in our study the lower dose of rivaroxaban was prescribed by 45.5% of rivaroxaban prescribers and the lower dose of apixaban was prescribed by 7.7% of apixaban prescribers. Moreover, for the given scenario 35.6% of Cardiologists preferred the low dose of dabigatran, whereas among internists it was 57.6%. For rivaroxaban, 50% of both Cardiologists and Internists used low dose. For apixaban, no Cardiologist preferred the low dose, but 14% of Internists prescribing apixaban preferred the low dose. It appears that the Internists are less likely to use the standard full dose of the NOACs compared to the cardiologists. This may be because the internists tend to be more concerned with the side effects of their treatment as reflected in our survey where 45.5% of internists cited safety as the main consideration, whereas only 22.2% of cardiologists did so. It highlights the need of more exposure of the internists to the need for appropriate dosing of the NOACs as the inappropriate low dose may not give the patients the added benefit of NOAC over VKA[7,8].

Limitations of the Study :

We studied the mindset of physicians when prescribing NOACs. Their actual prescribing pattern may differ depending on individual circumstances, where the cost of NOAC and patients' preference about compliance and availability of antidotes may modify their prescription. A larger sample size could have also made a difference to our results.

Conclusion :

Dabigatran was the NOAC most preferred by the physicians practising in Kolkata. The reason for choosing one NOAC over the others was largely driven by perceived efficacy and safety, rather than cost or availability of an antidote. Some differences exist between the practice of the Cardiologists and the Internists. The survey also opens up the issue of inadequate or inappropriate usage of the NOACs, which should be addressed for improving quality of patient care.

What is Already Known?

It is known that prescriptions for NOAC are gradually

increasing in the recent years. The mindset of doctors while prescribing NOAC in the real world is not known

What this Survey Adds ?

Dabigatran is the most preferred NOAC among the physicians of Kolkata. The reason for choosing one NOAC over others was largely driven by perceived efficacy and safety, rather than consideration for compliance, cost or availability of an antidote. Inappropriate dosage of NOAC prescription is a matter of concern among both Internists and Cardiologists.

Conflict of Interest : None

Sources of Research Support Including Funding, Equipment, And Drugs : None

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Original Article

Clinical profile and outcome of pediatric diphtheria cases admitted at a tertiary health care centre

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Objective : To study the clinical profile and outcome of pediatric clinical diphtheria patients admitted at a tertiary health care center.

Methods : A hospital-based prospective study was conducted in all clinically suspected diphtheria cases of pediatric age group, admitted in the pediatric isolation ward of tertiary health care and referral center from January 2015 to December 2018 (4 Years). Cases were diagnosed with detailed history, clinical examination and throat swab examination for Albert stain and culture. All cases are treated using the standard protocol.

Results : 46 diphtheria cases were enrolled who met the case definition of clinical diphtheria (consistent clinical symptoms with a sore throat, fever, cough, etc. with membranous tonsillitis). The majority of cases were between 09 to 11 years (43%); 60% were females. Most of the cases reported in September-October (44%). Poor immunization coverage is noted (90%) where 63% were unimmunized. Fever, cough and sore throat are predominant symptoms (93%) whereas dysphagia, stridor and bull neck were correlated with poor outcomes. Albert staining, as well as culture, showed good results. Amongst 46 patients, 08 patients were referred to higher centers owing to the unavailability of ADS. The outcome was satisfactory with total recovery in 78% while fatal in 03 cases (case-fatality rate: 8%).

Conclusions : Shift of age group, poor immune status, early diagnosis, and effective treatment showed good cure rates. Immunization status of each child should be actively enquired and catch up immunization should be promoted. A high index of suspicion towards diphtheria is required and early treatment should be initiated.

[*J Indian Med Assoc* 2020; **118(9):** 41-3]

Key words **: Corynebacterium diphtheriae, Diphtheria, Diphtheria in children, Pediatrics diphtheria.**

Since ancient times, diphtheria has been one of the deadliest and one of the most feared infectious disease globally. It caused many devastating epidemics mainly affecting children[1]. Diphtheria is an acute infectious disease of the upper respiratory system ie, nasal, oropharyngeal and laryngeal. It is caused by toxogenic strains of *corynebacterium diphtheria. It is* fatalunless identified in the early course of the disease and treated. Still it is preventable as the highly potent and immunogenic vaccine is available. Due to poor routine vaccination coverage, still, it is a significant health problem in developing countries. Although Globally, the incidence of diphtheria has decreased dramatically due to effective childhood vaccination programs. During 2001-2005, nearly half of the diphtheria cases reported globally were from India and between 2011-2015 India had the largest total no of diphtheria cases reported worldwide. India accounted for more than 71% of the total of 4880 cases in the world in the year 2011[3]. Because of the significant proportion of the global burden of this deadly disease with many outbreaks reported in the recent past, India can be termed as the capital of diphtheria. There has been a re-emergence of diphtheria in many developing countries with low vaccine coverage and

Editor's Comment :

- **Tonsillar Diphtheria is the commonest type in children.**
- **Early diagnosis and administration of Antidiphtheric serum results in a good outcome.**
- **Vaccination history should be enquired for any case of membranous tonsillitis.**
- **A high index of suspicion is required for early diagnosis, treatment, and a better outcome.**

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Received on : 31/01/2020
Accepted on : 01/07/2020

waning vaccine immunity in developed countries too. The number of cases reported to the World Health Organization has declined from 1,00,000 cases in 1980 to 2,500 cases in 2015. A similar decline was seen in India though India accounted for the majority of diphtheria cases globally.

In studies from states like Andhra Pradesh, Assam, Karnataka, Maharashtra, Rajasthan, Uttarakhand, and West Bengal, >50% of diphtheria cases were aged >5 years. According to the national level health surveys (NFHS 4- 2015-16), the coverage of 3 primary diphtheria vaccines ranged between 55.1 % and 78.4 % ie, just more than half of all children aged 12-36 months fully vaccinated with UIP recommended vaccines. The 5-year coverage of BCG and DPT3 in Indian children was 87% and 63% respectively. There is a reappearance of microbiologically confirmed cases of diphtheria in many parts of India. Poor immunization coverage, population migration, and overcrowded slums may be the etiological factors[2]. The diphtheria toxin binds to various cells in the body including epithelial, nerve and muscle cells. After binding it interferes with enzymes necessary for protein synthesis leading to cell damage and ultimately cell death[4].

Materials and Methods

A hospital-based prospective study was conducted at Shri Bhausaheb Hire Government Medical College and Hospital, Dhule, Maharashtra, India, a tertiary care and referral center from Jan 2015 to Dec 2018. All clinically suspected cases of diphtheria, admitted in pediatric isolation ward were diagnosed with detailed history, clinical examination who met the case definition of clinical diphtheria (consistent clinical symptoms with a sore throat, fever, cough, etc. with membranous tonsillitis) and throat swab examination on Albert stain and Culture (Table 1). All cases were treated by using a standard treatment protocol. Inj Crystalline Penicillin in a dose of 2 lakh units per kg body weight in 4 divided doses i.v. after the skin sensitivity test for 14 days. Inj. Anti-Diphtheric Serum (ADS) given after skin sensitivity test as an intravenous infusion over 30 to 60 minutes. It was given in the dose of 40,000 units for mild nasopharyngeal lesions, 80,000 units for pharyngeal or laryngeal lesions of 2 days duration and 1,20,000 units for pharyngeal and laryngeal lesions with obstruction of airways or longer than 2 days duration. The child was vaccinated as per his / her previous immunization status according to national guidelines. Household susceptible contacts received erythromycin for 7 days. The data was entered in Microsoft excel, statistical tests were done by proportions and chi-square test.

Results

The chi-square statistic is 2.9858. The p-value is 0.083998. This result is not significant.

The chi-square statistic with Yates correction is 2.286. The p-value is 0.130546 and is not significant. No significant difference between the two tests.

Discussion

In older studies like Patel UV *et al* (2004)[5] the predominant age group was under five, the percentage was 61.9%. The median age of diphtheria cases in most of the recently published studies was >5 years. In our study, >90% of cases were ≥5 years of age. That is consistent with many recent studies done in states like Andhra Pradesh, Karnataka, Maharashtra, Rajasthan, and West Bengal[2]. In a study by Talsania N *et al* (2011) 47% of cases were of the age group of 10-19 years age group[6]. The occurrence of diphtheria cases in under-five children reflects low coverage of primary diphtheria vaccination. There was a high proportion of cases in under-fives during the prevaccination era globally as well as during the eighties in India due to lower vaccination coverage. Nowadays higher median age of most of the diphtheria cases in India indicates good primary vaccination coverage protecting under-five children at the same time increasing susceptibility of school-going and adolescent children to either on account of low coverage of diphtheria vaccines as well as declining immunity acquired by vaccination or naturally. Hence the age distribution of diphtheria cases

Table 1 — *The socio-demographic characteristics, clinical features and outcome of the study participants*

Demographic parameters		N (%)
Sex	Male	19 (41.3)
	Female	27 (58.7)
Age (in Years)	<5	3 (6.5)
	5-10	25 (54.3)
	11-15	14 (30.4)
	16-20	4 (8.7)
Clinical Features		N (%)
Fever	Present	43 (93.5)
	Absent	3 (6.5)
Cough	Present	44 (95.7)
	Absent	2 (4.3)
Stridor	Present	44 (95.7)
	Absent	2 (4.3)
Dyspnoea	Present	9 (19.6)
	Absent	37 (80.4)
Immunization Status	Immunized	4 (8.7)
	Unimmunized	17 (37)
	Partly Immunized	8 (17.4)
	Not Known	14 (37)
Epiglottitis	Present	3 (6.5)
	Absent	43 (93.5)
Bull Neck	Present	5 (10.9)
	Absent	41 (89.1)
Sore Throat	Present	44 (95.7)
	Absent	2 (4.3)
Microscopy	Positive	33 (31.7)
	Negative	13 (28.3)
Culture	Positive	25 (54.3)
	Negative	21 (45.7)
Outcome	Cured	30 (65.2)
	Referred to Higher Centre	7 (15.2)
	AMA	6 (13.0)
	Died	3 (6.5)

reflects the immunity status of the community. In our study, it indicates good primary vaccination coverage so shift of age group (ie, attack rates are lowest among infants, increasing with age, and reaching to its maximum among children of 10-14 years of age) in Dhule district and adjacent area. In a study by Phalkey RK et al.[7]In one surveillance study by Verma S *et al*, 2019 the median age of diphtheria cases was 5-9 years of age[8]. The coverage of the primary diphtheria vaccine in the country is around 80%, whereas, the coverage of diphtheria boosters is expected to be low[9]. In countries with temperate climates, most diphtheria cases occur during the cold months but in warmer climate countries, the transmission takes place throughout the year[1]. In our study, >54% of cases occurred in winter months – from October to January (Table 2). In a study by Ray SK *et al* (1998)[10], Bildhaiya GS *et al* (1972)[11] majority of the cases were admitted in August to October. In a study by Phalkey RK *et al*[7], 82% patients had a cough, 73% had a low-grade fever, 64% had throat congestion, 64% had pseudo-membrane, 45% sore throat, 36% tonsillar patch, 27% dysphagia, 18% Bull neck (neck swelling) and 9% cases had difficulty in breathing, stridor and nasal discharge (Table 1).

The case fatality rate in our study was 8% that is comparable with 9% in a study by Phalkey RK *et al*[7]. Mortality is associated with poor immunization coverage and waning immunity over time. Early diagnosis and active treatment of the diphtheria cases will reduce the mortality. In a study by Patel UV *et al*[5], case fatality was nil in completely immunized patients, 21.4% in partially immunized patients and 28.2% in unimmunized patients. Most of the diphtheria cases were unvaccinated. In our study 37% of cases were unvaccinated and 37% with unknown status, 17% partially immunized and 8.7% were immunized. In a study by Patel UV *et al*, 2004[5] only 3% of patients were fully immunized, 30.8% partially immunized and 65.4% were unimmunized. It is in consistent with the increasing trend of vaccination in India and Maharashtra.

Table 2 — *Distribution of cases according to Years and Months*

Year	2015	23 (50.0)
	2016	12 (26.1)
	2017	2 (4.3)
	2018	9 (19.6)
Months	January	7 (15.2)
	February	2 (4.3)
	March	2 (4.3)
	April	4 (8.7)
	May	1 (2.2)
	June	0 (0)
	July	2 (4.3)
	August	5 (10.9)
	September	5 (10.9)
	October	11 (23.9)
	November	3 (6.5)
	December	4 (8.7)

Which test is better?

	Microscopy	Culture
Positive	33 (29) [0.55]	25 (29) [0.55]
Negative	13 (17) [0.95]	21 (17) [0.94]

Recommendations

Receiving the fourth and fifth doses (first and second boosters) is needed for complete protection against diphtheria. Hence coverage for the booster doses should be improved. As in many studies, the common age group is >10 years, it is better to change TT with Td which is administered in adolescents at the age of 10 and 16 years according to the National Immunization schedule.

Funding : None

Conflicts of interest : None

Contribution Details

Hatkar NK - Concept and Design, acquisition of data, analysis, and interpretation of data.

Rathod KG- Definition, Literature search, drafting the article and revising it critically.

Salunkhe YM-final approval of the version to be published.

Mohd. Ubaid ur Raheman – Statistical Analysis.

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JOURNAL OF THE INDIAN MEDICAL ASSOCIATION, VOL 118, NO 09, SEPTEMBER 2020

Original Article

Results of Philos Plating In Adult Proximal Humerus Fractures

Sumit P Prajapati[1], Anil Kumar J Nayak[2], Mahesh R Khandelwal[3]

Being the most common fracture of the shoulder girdle, proximal humerus fractures occurs more common in elder age group attributing to osteoporosis. Involvement of younger age groups and complex patterns of proximal humerus fracture are more common at present in these fractures due to incresed incidence of high velocity trauma and vehicular accidents. Clinical outcomes can be bothersome to patients and their daily activities of life and their management often demands high level of surgical skills. Using PHILOS plate for open reduction and internal fixation of these fractures, we have studied and evaluated the functional and radiological results. Methods & material: We retrospectively reviewed 20 patients who were operated for proximal humerus fracture by PHILOS plate by deltopectoral and deltoid split approaches between 2014-2017. Preoperative xrays and in some cases CT scans were done. Postoperative x-rays were evaluated and Constant shoulder score was used as a clinical tool for assessment.

Results : In a mean follow up period of 50 months, 55% patients showed excellent and 25% showed good outcome with improved Constant Shoulder Score. 1 patient encountered infection with resultant stitch gaping and nonunion, 2 patients had malunion, and 1 patient developed AVN of humeral head. 2 patients had to change their occupation post operatively. No patient had conversion to total or hemi arthroplasty till last follow up. Conclusion: 2-,3- and 4-part proximal humerus fractures and fracture dislocations by Neer's classification treated by PHILOS plate by open reduction and internal fixation give gratifying results with early mobilisation exercises and physiotherapy with low complication rates.

[*J Indian Med Assoc* 2020; **118(9):** 44-7]

Key words **: PHILOS, Constant shoulder Score, Neer's classification, Open reduction internal fixation, Vehicular accident, Deltopectoral approach, Deltoid split approach, AVN, Early rehabilitation.**

Osteoporosis and poor bone stock are usually the attributing factor for proximal humerus fractures[1,2] and are mostly caused by low energy trauma. There is universal agreement that most stable fractures, which often occur in frail, elderly patients, are best treated nonoperatively. Involvement of younger age groups and complex patterns of proximal humerus fracture are more common at present in these fractures due to incresed incidence of high velocity trauma and vehicular accidents[3]. Different modalities of treatment are available and best possible treatment option depends on patient's age, quality of bone, surgical expertise, needs and expectations of the patient. These fractures affect daily activities of human life. Different treatment protocols are available with supporting as well as contradicting evidences of their own. Treatment modalities of wide range have been used in past ranging from percutaneous pin, wire and screw fixation, transosseous suture fixation, tension bend wiring, standard plate fixation to hemire placement arthroplasty[4-6]. Using PHILOS plate for open reduction and internal fixation of these fractures, we have studied and evaluated the functional and radiological results.

Editor's Comment :

- **The PHILOS plate due to stable fixation allows to regain better shoulder function and early return to activities in Neer's 2-part, 3-part and 4-part fractures.**
- **Complication rates with this technique are low in present study.**
- **Early mobilization exercises and physiotherapy yielded better movements of operated shoulder.**
- **Present study showed gratifying results with PHILOS plating in Neer's 2-part, 3-part and 4-part fractures.**
- **Larger sample size with more 4-part fractures will help yield more accurate results of this treatment for more complex fracture patterns.**

Materials and Methods

We retrospectively reviews 20 patients who were operated for proximal humerus fracture falling in Neer's classification 7 of 2-PART, 3-PART, 4-PART with

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Received on : 18/08/2020
Accepted on : 03/09/2020

PHILOS plating between 2014-2017 of which 14 patients were operated by DELTOID SPLIT and 6 patients were operated by DELTOPECTORAL approach[8]. According to NEERs classification, 6(30%) patients had 2-part, 12(60%) patients had 3-part and 2(10%) patients had 4-part fracture. Patients with any of the following were excluded: medically unfit, fracture in <18 years of age, shaft humerus fracture with proximal extension, Neer's classification 1-part fracture, open fractures, associated with neurovascular injuries. Patients were explained about procedure, prognosis and informed consent was taken. Total 20 patients comprising of 15 males and 5 females with 70% patients falling in age group of 26-45 years were included with mean age found to be 41 years. One patient had early infection with resultant stitch gaping which was reoperated for debridement of wound and removal of screw and infection site. Fracture showed nonunion on follow up and was lost at follow up. One patient having 4-part fracture dislocation by Neer's classification with head split developed humeral head AVN resulting in arthritis. In 2 patients head was fixed in various and both the patient had malunion on follow up. 55% patients had RTA as mode of injury with most of the patient having age 30-45 years and 1 patient had railway accident. 40% of patients had associated injury to other limbs and systems as a result of high velocity trauma. Preoperative radiological evaluation of shoulder was done in all cases by X-ray Anteroposterior view and Axillary view and CT Scan in some of the patients. Postoperative shoulder Anteroposterior and Lateral views were obtained and Head shaft angle, nonunion, malunion, AVN of humeral head were assessed. After suture removal, follow up was done at monthly interval for 3 months, at 6 months and 6 monthly thereafter. Patient was assessed clinically and radiologically on every follow up.

Surgical approaches and procedure

14 patients were operated by deltoid split and 6 patients were operated by deltopectoral approach in supine position. The affected arm was draped to allow free motion intraoperatively. Injectable intravenous antibiotic ceftriaxone and sulbactam were administered half hour prior to surgery. Head end of patient was put on radiolucent part of the table such that standard intraoperative Anteroposterior and Lateral views were possible throughout the procedure.

Deltoid split approach[8] —

The skin incision follows direction of muscle fibres along upper part of deltoid at junction of anterior and middle raphe. Starting from the acromion, deltoid muscle is split along its fibres taking care not to injure axillary nerve.

Deltopectoral approach[8] —

Oblique incision 15cm starting from below clavicle passing over the coracoid. Deltopectoral groove and cephalic vein identified and conjoint tendon retracted. Biceps tendon was located. Greater and lesser tuberosity fragments were identified with their tendon attachments relative to biceps tendon.

The rest of the surgical techniques applied did not differ between both groups. Articular fractures were anatomically reduced. Greater and lesser tuberosity fractures were reduced by fixing rotator cuffs with ethibond suture. After provisional fixation with k wires, final fracture fixation was done with PHILOS plate (Fig 1).

Postoperative Rehabilitation

During immediate postoperative period, shoulder and elbow were kept in immobiliser and finger, wrist mobilization exercises were allowed. Patient was kept immobilised in shoulder immobiliser till the condition required. Pendulum exercises were started as soon as the patient felt comfortable. After 3 weeks, forward flexion upto 90° and abduction upto 90° started. After 6 weeks, overhead abduction and external rotation were allowed and encouraged. Weight lifting was allowed once union was confirmed clinicoradiologically on follow up.

Results

Our mean follow up period was 50 months comprising 15 male and 5 female patients with mean

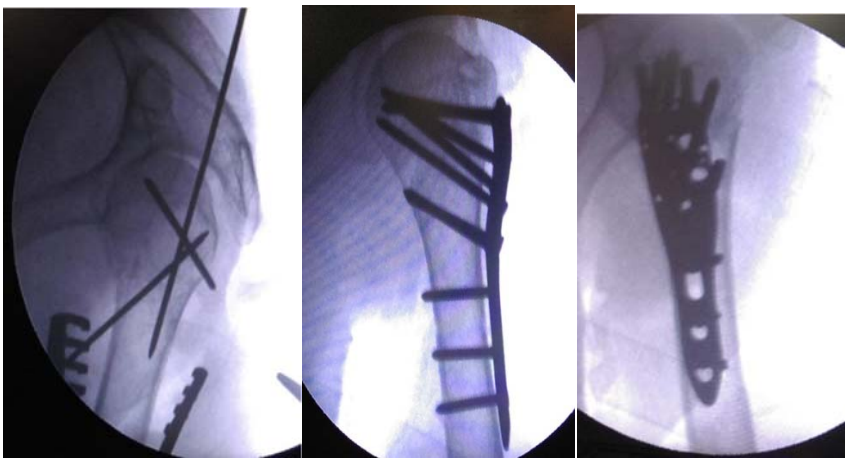

Fig 1 — Provisional fixation of fracture with k wires followed by fixation with plate

age 41 years. The age and sex distribution of study population is given below in Table 1.

As is evident, majority of the patient belong to age group 26-45 years comprising 70% of study population.

We have used constant shoulder score (CSS)9 as clinical tool to measure results in our patients. CSS is measured at 3 months postoperatively and thereafter at interval of 6months. The given table features CSS (difference between normal and abnormal side) in follow up patients (Table 2).

As is evident, in age group 26-45 years 11 out of 14 patients and in age group 46-65 years 5 out of 6 patients had excellent to good CSS.

Only 1 patient had non union and in all the united fractures, clinical union preceded radiological union with clinical and radiological union seen at mean 9 and 10 months respectively (Tables 3&4).

As is evident, 1 patient had infection with resultant stitch gaping which was treated by antibiotics and regular dressing and required delayed suture removal. This patient was then re-operated for debridement of wound and removal of one screw at the infection site. The fracture had head split and showed nonunion on follow up. This patient was lost at follow up.

One patient developed humeral head avascular necrosis which further caused arthritis. The fracture pattern was 4 part fracture dislocation by Neer's classification with head split. In 2 patients humeral head was in various fixation and had malunion on follow up. These complex patterns of fractures could be the reason for the radiological complications. These patients had restriction in movements and overhead abduction was not possible.

Table 1 — *Age and Sex distribution of study population*

Age Group (in Years)	Male	Female	Percentage
26-35	10	1	55%
36-45	2	1	15%
46-55	2	1	15%
56-65	1	2	15%
Total	15	05	100%

Table 2 — *Constant Shoulder Score*

Score Rating	26-45 Years	46-65 Years	Percentage
Excellent (<11)	8	3	55%
Good (11-20)	3	2	25%
Fair (21-30)	1	0	5%
Poor (>30)	2	1	15%

Table 3 — *Union Frequency*

Weeks	Radiological Union		Clinical Union	
	Number	Percentage	Number	Percentage
8	0	0%	13	65%
10	16	80%	5	25%
12	3	15%	1	5%
14	0	0%	0	0%
16	0	0%	0	0%
18	0	0%	0	0%
20	0	0%	0	0%

Table 4 — *Complications*

Complication	Number	Percentage
Early Infection	1	5%
Stitch Gaping	1	5%
Malunion	2	10%
Nonunion	1	5%
Avn	1	5%

Discussion

Non operative treatment of Neer's 3 and 4 part fractures of the proximal humerus is associated with poor outcome due to intraarticular fracture geography and inherent instability of fracture fragments[10,11]. Screw loosening, fracture redislacement, fixation failure are more common in comminuted fractures. Careful assessment of the patient in terms of age, bone quality, fracture type, comminution, activity level and patient's needs is required before deciding the type of treatment in particular patient. Good bone quality, minimal comminution of fracture, compliance of patient and expertise n skills are required for better results with percutaneous pinning[6,12-14]. Complications like loosening of screws, subacromial impingement or humeral head avascular necrosis[15-18]. Extensive stripping of soft tissues are needed during open reduction of these fractures which further compromises vascular supply of humeral head. Chances of axillary nerve and vascular damage are more with minimal invasive methods of osteosynthesis plating of proximal humerus fracture[19,20] PHILOS provides better angular stability. Multiplanar placement of screws in humeral head with locking of screws with plate at fixed angle gives advantage of high resistance to back out. Shorter period of immobilization and early beginning of rehabilitation are other advantages of PHILOS plate attributable to initial better stability with fixation[21,22]. In our study 80%(n=16) of the patient had excellent to good outcome. Functional outcome was better in 2- and 3- part fracture. With 50.85% patients of 2-part and 3-part fracture and 49.15% patients of 4-part fractures and mean age of 42 years, Mohammed M.H. El-Sayed in their study showed 69.5% excellent to good results[23]. 31.8% 3-part and 4-part fractures in mean age of 63 years Parmaksizoglu et al found 68.7% excellent to goid result[24]. Epidemiology of proximal humerus fracture shows younger age group of patients with increase in frequency of more complex fracture patterns due to increased frequency of vehicular accidents and high velocity trauma in younger active population[3]. Even with satisfactory shoulder function the functional outcome may be lower than expected

due to associated injuries. Varus collapse is associated with restriction of range of motion and poor functional results. This study showed lower complication rates. Early rehabilitation and physiotherapy of operated shoulders gave better range of motion.

Limitation of our study : It was limited number of patients and even less 4-part fractures. Technical expertise, adequate exposure to complex fracture patterns and high level of surgical skills give more promising results.

Funding : None

Conflict of Interest : None

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Image in Medicine

Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

Questions :

(1) What are the CT chest patterns seen in COVID-19 pneumonia ?

(2) What is CORADS?

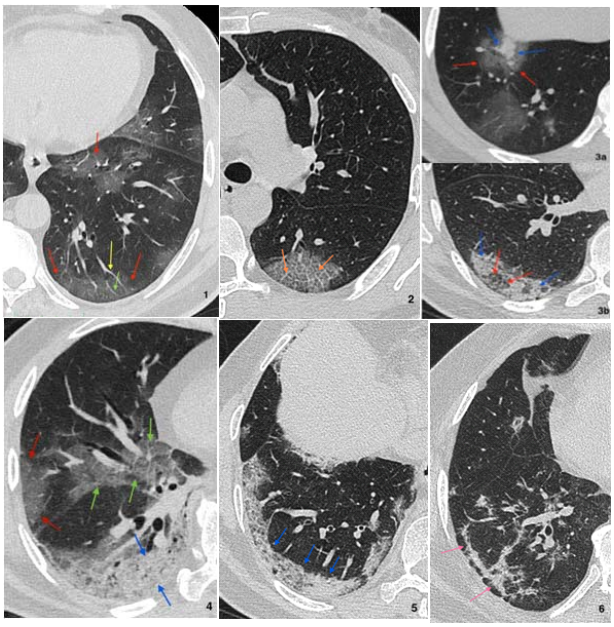
(3) What is CT chest severity score?

Answers:

(1) COVID-19 pneumonia typically presents with ground glass opacities (Fig 1), which can be associated with reticular opacities / septal thickening, giving rise to "crazy-paving pattern"(Fig. 2). It can also present as ground glass halo around consolidation (Fig. 3a) or ground glass in the centre with rim of consolidation ("atoll sign") (Fig. 3b). Mixed pattern (Fig. 4) can also be seen which is a combination of consolidation (Fig. 5), ground glass and reticular opacities with or without architectural distortion. Subpleural band like opacities (Fig. 6) are often seen later in the course of disease, giving an appearance of an organising pneumonia pattern. Prominent proximal (Fig.1- yellow arrow) or intra-lesional dilated vessels (Fig. 1- green arrow) in the areas of ground glass opacities is a sign that helps to differentiate COVID-19 from other conditions.

(2) CO-RADS is a standardized reporting system, used in most CT scan reports to communicate the level of suspicion of COVID-19 infection, based on the CT findings. CO-RADS 1 - Unlikely, CO-RADS 2 - Low, CO-RADS 3 - Indeterminate, CO-RADS 4 –High suspicion, CO-RADS 5 – Classic findings.

(3) The severity of lung involvment on CT scan is



scored as percentage of each of the five lobes that are involved. [< 5% involvement - 1 / 5%-25% involvement - 2 / 26%-49% involvement - 3 / 50%-75% involvement - 4 / >75% involvement. – 5]. The total CT score is the sum of the individual lobar scores.

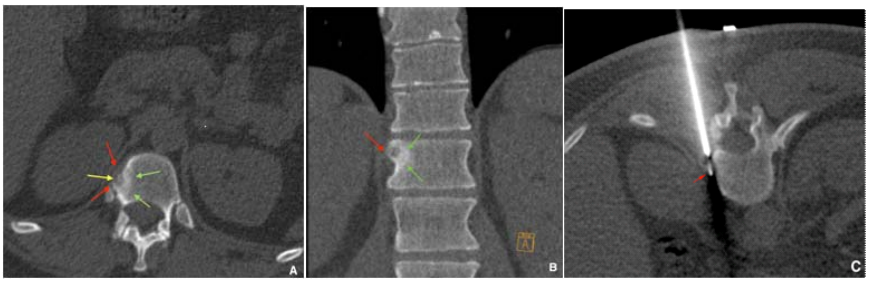
Quiz 2

Questions:

(1) What is the diagnosis?

(2) What are the common locations of the lesion?

(3) What is the treatment of choice?



A 31year old man presented with severe back pain, relieved by salicylates.

Answers:

(1) Osteoid osteoma — Well defined cortical based lesion showing a small osteolytic / lucent nidus (red arrow) with surrounding sclerotic reaction (green arrow) is seen involving the right lateral margin of D12 vertebral body. A central region of mineralisation (yellow arrow) is seen within the nidus.

(2) Osteoid osteomas commonly occur in long tubular bones (femur – especially neck, mid tibial diaphysis), phalanges and vertebrae.

(3) CT guided radiofrequency ablation (RFA) is a safe, effective and method of choice treatment of osteoid osteoma (Fig C).

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

Student's Corner

Become a Sherlock Homes in ECG

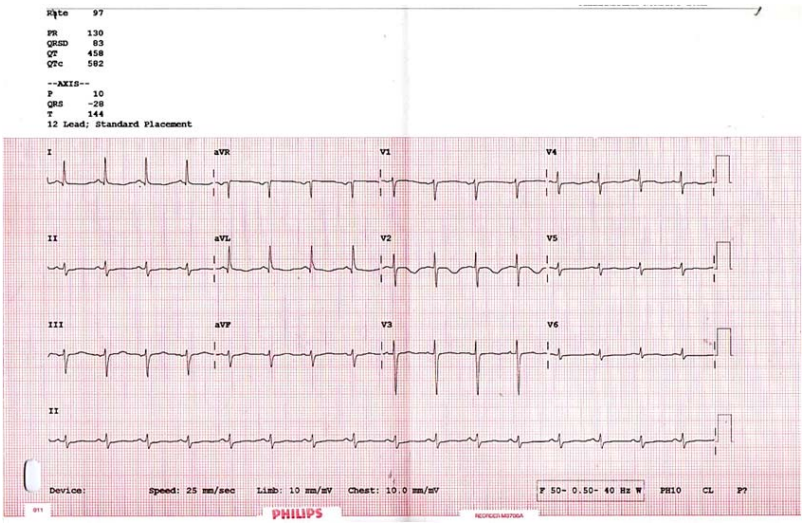
M Chenniappan[1]

Series 4 :

ECG

"Low but High"

This is the ECG of 65 years old diabetic lady who has undergone non-cardiac surgery recently, after an episode of seizures.



Questions :

1. Describe ECG changes.
2. Why is this Clue ?
3. What are Practical implications ?

Answers :

(1) ECG Changes :

This ECG shows, sinus rhythm, Minor ST T changes, left ward axis, but not typical LAFB (rs in LII) in limb leads. In chest leads, there are non-progression of R waves, significant T inversion in V2, minor ST T changes in other leads, and low voltage QRS complexes in lateral leads. The significant finding in this ECG is QT interval prolongation (QTc 582m.sec.). This ECG is after an episode of seizures in a diabetic lady. In the presence of long QTc with seizures, most often TorsadesDe Pointes (TDP) is suspected and investigation as well as treatment are planned in these lines. But, one common problem is most often not thought off. That is hypoglycemia. Hypoglycemia can produce significant ECG changes due to significant abnormalities in the heart due to hemodynamic, metabolic, vascular, autonomic and electrophysiological abnormalities. The QT interval can be significantly prolonged due to catecholamines and hypokalemia which can further lead on to TDP. So, without correcting hypoglycemia, treatment for TDP alone is not useful, but dangerous as it may not respond and may progress to VF and Cardiac arrest. This patient's blood sugar was 20mg/dl which was corrected immediately and the ECG was taken as soon as the seizures were controlled and this showed long QTc. This patient's pre- and post-operative ECGs did not show long QTc. The non-progression of R wave is probably due to mal positioning of ECG leads because of abdominal surgery. The ECG changes in hypoglycemia are listed below :

ECG changes in hypoglycemia

- ST depression
- T flattening
- Prolonged QT
- Atrial and ventricular arrhythmias
- Primarily due to catecholamines and hypokalemia
- Probable mechanism for **"Dead In Bed Syndrome"** in young diabetics

(2) Why is this clue ?

This patient had low blood sugar because of which there was high QT interval (QTc prolongation). That is why the clue of **"Low but high"**is given.

(3) Practical Implications :

Most often in hypoglycemia, we think of brain and not the heart. As soon as patient becomes conscious, it is very important to record ECG for long QT as well as acute ischemic changes, which are most often missed and may produce life threatening events subsequently even after correction of blood sugar. So, don't forget to record ECG after the treatment of hypoglycemia.

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Case Report

An interesting and rare presentation of Autoimmune Hemolytic Anemia secondary to Systemic Lupus Erythematosus — A case report

Ronak Jain G[1], G Vijayalakshmi[2], T B Umadevi[3]

Initial Presentation of Systemic Lupus Erythematosus (SLE) in the general population varies among individuals, can be atypical and often very confusing to confirm or even suspect SLE in the early stage of the disease. With low index of clinical suspicion or inadequate follow up, the diagnosis of SLE could be delayed. Sometimes Autoimmune Hemolytic anemia(AIHA) can be the only initial symptom of SLE in a patient which should not be missed and when picked early could drastically improve the outcome and prognosis of the disease. We report an interesting case of SLE initially presenting as AIHA in a 13 year old south Indian girl.

[*J Indian Med Assoc* 2020; **118(9):** 50-2]

Key words **: Autoimmune haemolytic anemia, Thrombocytopenia, Anemia, Childhood, Systemic Lupus Erythematosus.**

Haematological disorders are frequently seen in systemic lupus erythematous (SLE). Anemia is found in 50% of all SLE cases and can be precipitated by multiple elements such as long standing disease, deficiency of iron, chronic kidney dysfunction, myelotoxicity induced by intake of drugs, and even autoimmune Hemolytic Anemia (AIHA)[1]. Much of the literature available on AIHA is from the west.SLE is rare in India. A prevalence analysis carried out in India (in a rural population near Delhi estimated a point prevalence of 3 per 100,000[10].

AIHA is seen in 5–10% of SLE cases[2]. AIHA can appear as an isolated initial manifestation at the onset of SLE diagnosis or during the first year of illness[3]. It is also linked with many forms of SLE manifestations such as lupus nephritis, thrombocytopenia and as well as higher index of disease activity and bad prognosis. With an incidence of 1-3 cases in 100,000[4,5] per year makes AIHA relatively rare and diagnosing AIHA to be secondary to SLE is a rare presentation of the disease itself which has a varied and unusual presentation.

Case Report

A 13 year old female from southern Tamil Nadu came with complaints of easy fatigability, abdominal distension and increased hair fall for the past 4 months. Her past history consisted of recurrent admissions for anemia in the past 4 months for which she was treated symptomatically. Her family and personal history were unremarkable. There was no history stating previous blood transfusions or bleeding manifestations. On examination, patient was thin built and poorly nourished. She was pale, icteric and had bilateral deep cervical lymphadenopathy. Oral cavity was normal with no ulcers. Hepatosplenomegaly was present. Viral markers were negative. Fundus examination showed changes suggestive of anemic retinopathy. Peripheral smear showed anisopoikilocytosis, reticulocytes with spherocytes and a reticulocyte production index of 3.3. USG showed hepatosplenomegaly with normal sized kidneys. We then did serum markers of hemolysis such as serum haptoglobin and serum LDH which was decreased and increased respectively. FNAC of the right cervical node was done which showed reactive lymphadenitis. Bone marrow aspiration showed a reactive erythroid hyperplasia which all pointed towards a haemolytic picture. Direct Coombs test (DCT) was positive. Serum C3 & C4 levels were low. ANA was then done which turned out to be positive and then ENA profile was carried out which was dsDNA positive and a diagnosis of AIHA secondary to SLE was confirmed. Since Proteinuria was present biopsy of the kidney was done which showed Class 4 Lupus Nephritis characteristically showing wire loop lesions (Figs 1-3).

Editor's Comment :

- **The most frequently seen acquired hemolytic anemia is AIHA.**
- **Anemia of Chronic Disease is the most common haematological presentation of SLE seen in 70% of cases[2].**
- **Hemolytic anemia (more commonly warm antibody/ Ig G type) is a rare presentation of of SLE seen only in 10% of cases[2].**
- **Any female patient in the reproductive age group with unexplained anemia should be evaluated for Autoimmune disorders specially SLE.**

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Routine investigations		Special investigations	
Haemoglobin	4.1g/dl	Serum LDH	1250 IU/L
Total count	6100/cu.mm	Serum Haptoglobin	10mg/dl
Differential count	N: 50% L:35% M:15%	Direct Coombs test	Positive
Platelets	1,21,000/cu.mm	Urine haemoglobin	Negative
MCV	108fL	Urine PCR	2.4
Serum urea	28mg/dl	Serum C3	50mg/dl
Serum creatinine	1.0mg/dl	Serum C4	15mg/dl
Total Bilirubin	3.1mg/dl	ANA	3+
Direct bilirubin	1.0mg/dl	dsDNA	Positive
Urine albumin	2+	Serum iron studies	Within normal limits
Other routine blood and urine parameters	Within normal limiits	Vitamin B12	500ng/L

Treatment

Patient was then started on 1 mg/kg per day of Prednisone along with Tab Mycophenolate Mofetil (MMF) 500mg OD (combination therapy for lupus nephritis), multivitamin, ferrous sulphate and calcium supplements and within 1 week she showed drastic improvements indicated by increase in haemoglobin and general wellbeing. At the time of discharge she was asymptomatic with lab parameters showing a Haemoglobin of 9.1g/dl and a platelet of 1,35,000/mm^3 She was discharged on T.Prednisone(0.5mg/kg/day), Tab MMF 500mg OD and T Hydroxychloroquine 200 mg OD along with vitamin supplements.

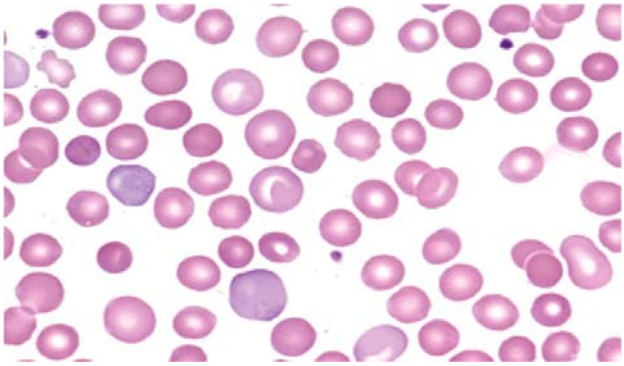

Fig 1 — Spherocytes, reticulocytes and Anisopoikilocytosis in peripheral smear Wright-Giemsa Stain, 200X

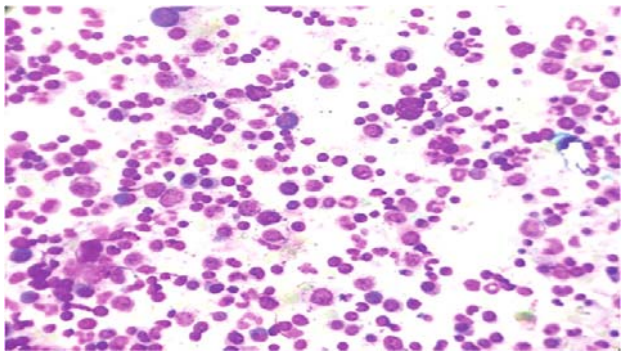

Fig 2 —

- Bone marrow aspiration showing erythroid hyperplasia suggestive of hemolysis. Myeloid to erythroid ratio is 1:3 which is reversed.Erythropoiesis is active and increased with erythroid hyperplasia.Myeloid series shows normal pattern of maturation.
- IMPRESSION: reactive erythroid hyperplasia showing micronormoblastic and normoblastic maturation
- Wright-Giemsa stain, 200x

Discussion

AIHA can be a primary or as in our case secondary to SLE. Autoimmune haemolytic anemia is an acquired disorder due to antibody mediated destruction of the RBCs. The most common type of anemia encountered in SLE is Anemia of Chronic Disease (ACD) which is seen in 60-80% of SLE patients. AIHA has been described in 4-10% of adult SLE which is relatively rare.

AIHA is characterized by elevated counts of reticulocytes, low levels of haptoglobin, increased concentration of indirect bilirubin and a positive direct Coombs' test. Warm/Ig G mediated AIHA accounts for 65-70% of the disease. Onset is sudden. Hepatosplenomegaly is present due to extravascular type of hemolysis. It is a serious condition and if untreated leads to 10% mortality.

The pathogenesis for AIHA in SLE involves erythrocyte damage mediated by antibodies, usually by warm-type IgG antibodies. The band-3 anion, a transporter glycoprotein of membrane erythrocytes, is also seen as a likely target[6]. Healthy people may also exhibit anti band 3 antibodies, and may help in clearing senescent erythrocytes, which when undergo aging reveal band 3 neoantigens. According to some authors, the antigenic neoepitopes, that are seen in these red cells may cause autoimmune mediated hemolysis[7]. Another pathogenic theory is cell lysis by complement activation commonly found in IgM mediated cold type AIHA causing an intravascular hemolysis[8].

The correlation between thrombocytopenia and AIHA has been documented in the past[3] and is also seen in our case. While the correlation between AIHA and the autoimmune thrombocytopenia called as Evan's syndrome might occur with other autoimmune diseases, it is identified more frequently in SLE[9]. This association proposes a

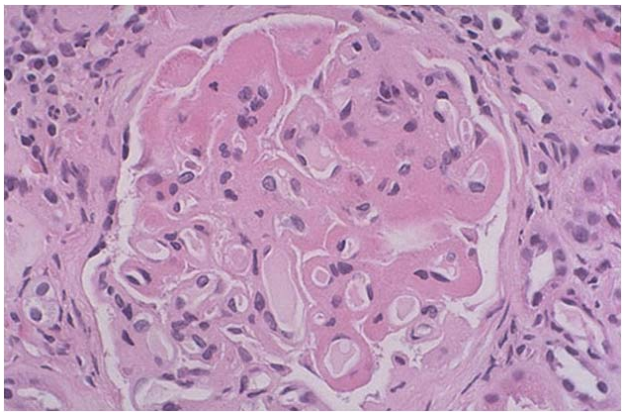

Fig 3 — Wire loop lesions in kidney biopsy characteristic of class 4 Lupus Nephritis, H & E stain, 400X

shared pathogenesis for these two manifestations, presumably involving antibody induced destruction of red blood cells, mostly mediated by warm antibodies of IgG type.

AIHA is treated with steroids as first line agents and second line treatment is with immunomodulators namely rituximab. Determining the cause of anemia is critical to treat the underlying disorder and preventing the progression of the disease to fatal complications such as renal failure. Anemia should never be overlooked because sometimes it can be the only symptom pointing towards a major underlying disorder such as in our case which turned out to be SLE. Whenever AIHA is diagnosed in a patient ,a full screen for autoimmune diseases (especially SLE) is imperative.

Lupus nephritis is a frequent and fatal complication of SLE. 30 to 50 percent of affected individuals will have clinical manifestations of kidney disease when the diagnosis of SLE is confirmed, and 60% of adults and 80% of children show renal defects at some stage during their illness[2]. Lupus nephritis develops from deposition of circulating immune complexes that activate the complement cascade resulting in complement mediated damage, infiltration of leucocytes, activation of procoagulant factors, and release of different cytokines.

Class IV defines universal, diffuse proliferative lesions involving the huge majority of glomeruli. Patients having class IV lesions usually have increased antiDNA antibody titers, serum complements are low, hematuria, red blood cell casts, hypertension, proteinuria and decreased renal function. Latest evidence recommends inducing remission by giving high dose steroids and either cyclophosphamide or MMF for 2–6 months, followed by maintenance therapy with lower dose of steroids, which balances the probability of successful remission with the side effects that may be seen with therapy.

Conflict of Interest : The author declares that they have no conflict of interest with respect to the authorship and/or publication of this article.

Limitations of Study : None

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Case discussion in Medicine

Adrenal Incidentaloma — Case based approach

Ravi Kant[1], Mukesh Kumar Bairwa[2], Mahendra Kumar Meena[3], Monika Pathania[4]

Adrenal incidentaloma is reported between 2-6% in radio-imaging, the lesions may be inactive or might secrete homones like glucocorticoid, mineralo-corticoid, sex steroid or at times catecholamines. The size of lesion is a determinant of nature of lesion, the larger ones are usually malignant, there is lot of gray area over the size of the lesion to classify as malignant but usually a lesion greater than 4 cm is taken a malignant. Radio-imaging by CT/MRI is a good initial investigation for characterization of lesion as adenoma vs non-adenomatous. Functional evaluation by radio-nucleide scan can differentiate between various sub-types.

[*J Indian Med Assoc* 2020; **118(9):** 53-6]

Key words **: Adrenal, incidentaloma, glucorticoid, mineralocorticoid, adenoma.**

Adrenal Incidentaloma is a common radiological accompaniment, its work up, diagnosis and management poses potential challenges and is quite confusing. The current case based approach will definitely aid in the evaluation of adrenal incidentaloma.

Case Report

A 68 -year-old lady presented with complaints of acute onset haematuria. It was insidious in onset, painlessdark coloured, moderate amount, with no history of loin/ abdominal pain and urinary symptoms like dysuria, polyuria, intermittency and hesitancy. She was evaluated for the above symptoms by a physician and a couple of investigations were advised along with abdominal ultrasound . Abdominal ultrasound showed a right adrenal mass measuring 3cm with no other abnormality detected and Endocrinology consult was sought for further evaluation of the adrenal mass with haematuria.

Q1. How to proceed for further history and examination ?

History of present illness : On further enquiry about the other symptom complex, she denied any history of excessive weight gain, central obesity, easy bruising, purplish stria, generalised weakness or paroxysmal muscular weakness, increased hair growth over body, recent onset of hypertension and /or glucose intolerance-ie, features suggestive of **glucocorticoid excess.**

She gave no history of paroxysms of headache, excessive sweating, palpitations suggestive of catecholamine secreting adrenal tumour like **pheochromocytoma.**

She had her menopause at the age of 50 years and denied any history of excessive facial hair growth, skin changes like acne, deepening of voice, clitoromegaly, male pattern baldness – features suggestive of **androgen secreting adrenal tumour**;

Also there is no history of vaginal bleeding and breast tenderness – features suggestive of **oestrogen secreting adrenal tumours**. She also deniedany history of easy fatigability and weight loss.

There was no family history of any intrabdominal mass; paroxysmal symptoms of hypertension, palpitations, headache; haematuria; renal tumours; excessive weight gain with increased hair growth over body/face. There is no history of anorexia, nausea, vomiting and weight loss

Past history : In past she suffered from transient ischemic attack 3 years before and recovered completely.

She underwent excision of malignant melanoma at upper back 5 years before. There is no other chronic illness like hypertension, diabetes mellitus or chronic infections like tuberculosis.

Family history : None of her family members suffered from adrenal tumour or melanoma

Drug history : She was currently on Clopidogrel for an episode of TIA

Editor's Comment :

- Adrenal incidentaloma is being more commonly diagnosed due to better radio-imaging, its clinical suspicion requires meticulous work up and treatment.

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Received on : 13/08/2020
Accepted on : 19/08/2020

Examination —

The general survey revealed hyperpigmentation of skin at the upper back at the excision site of malignant melanoma. She was moderately built and nourished. She had a weight of 160 pounds with a height 5 feet 10 inches metre and BMI : 23kg/m^2, HR- 76/min, supine BP-144/76 mmHg and standing was 138/80 mmHg.

She had no features of Cushing's syndrome – facial plethora, wide violaceous striae on abdomen,thighs or other places, no cuticular atrophy, bruises or proximal myopathy. Her Ferriman- Gallwey scoring was 8/30 and had no features of virilization. There was no acne, temporal recession of hair, low pitched voice, and clitoromegaly.

Systemic examination was normal with nolocal abdominal tenderness/ renal angle tenderness and no palpable abdominal mass.

By history and physical examination, it is more likely that patient has adrenal incidentaloma. Though she lacks the usual stigmata of overt Cushing's syndrome, Subclinical Cushing's syndrome is the commoner presentation amongst the symptomatic adrenal incidentaloma cases followed by Pheochromocytoma and Primary aldosteronism.

Q2. What are probable differential diagnosis?

Differential diagnosis :

1. Adrenal adenoma (Lipid rich)
2. Lipid poor adrenal adenoma
3. Pheochromocytoma
4. Sub clinical autonomous cortisol hypersecretion (Subclinical Cushing's syndrome)
5. Cushing's syndrome
6. Conn's syndrome
7. Carcinoma
8. Metastases
9. Hemangioma
10. Adrenal deposits
11. Ganglioneuroma
12. Tuberculosis
13. Adrenal cyst
14. Myelolipoma

Q3. How to plan further investigations to arrive to narrow diagnosis.

Investigations :

All patients with adrenal incidentaloma should be evaluated for hormonal hyperfunction, 85% are however non-functional[1]. It is important to rule out pheochromocytoma as it can lead to hemodynamic instability even in asymptomatic patients, more so at the time of surgery[2]. Following tests are to be done in cases of adrenal incidentaloma.

A. Biochemical assessments, Electrolytes and Arterial Blood gas analysis : Serum potassium levels vary with aldosterone level, a higher aldosterone level is associated with hypokalemia and metabolic alkalosis whereas a low aldosterone is associated with hyperkalemia and metabolic acidosis.

B. Specific tests for assessing adrenal gland functioning

1. Catecholamines and Metanephrine assessment : Twenty-four hours urinary free catecholamines or metanephrines is a good screening test to rule out pheochromocytoma. It is proven that plasma free metanephrines estimation is diagnostically superior to urinary catecholamines and/or metanephrines, but it's use in diagnosis is limited due to its non-availability at many centers.[3] Currently the diagnostic utility of plasma catecholamines and metanephrines lie in cases where the urinary levels of these compounds are normal and the clinical suspicion of pheochromocytoma is high.

2. Primary aldosteronomas : Primary aldosteronomas (PA) are found in 1.5-3.3% in adrenal incidentaloma. Screening is recommended for hypertensive patients.[4] Almost 40% of patients with PA have normal serum levels of potassium and hypokalemia is not a reliable sign to investigate PA.[5]The diagnostic armamentarium for Conn's syndrome as suggested by Barts is as given in Table 1.

3. Cortisol estimation: There is increasing evidence that there is abnormality in hypothalamo-pituitary-adrenal axis in patients with adrenal incidentaloma even in otherwise non-cushing's patients, better known as sub-clinical autonomous

Table 1 — *Depicting the diagnostic criteria for conn's syndrome*

Conn's: case confirmation			
Confirmatory test	Procedure	Interpretation	Points of note
Oral sodium loading test	200 mmol (6g)/d for 3d Maintain normal K+-24 hr urinary aldo d3-4	PA unlikely if aldo excretion <10µg/dl (27.7nmol) PA likely if >12 mg/d (33.3nmol)	Avoid in cardiac/ renalfailure; uncontrolled hypertn
Sodium infusion test	Infuse 2L saline over 4 hrs Patient recumbent - Samples for K+, cortisol, aldo and renin at 0 and 4 hrs	<5 ng/dl PA unlikely; >10ng/dl PA likely; 5-10ng/dl indeterminate	Avoid in cardiac/ renal failure; uncontrolled hypertn
Fludrosupprn test	FC 0.1mg 6 hrly for 4d Keep K+ normal NaCl – generous PRA and aldo at 1000H on d4 Cortisol at 0700 and 1000H	Upright aldo on d4 >6ng/ml confirms PAPRA must be <1ng/ml/hrCortisol at 1000 should be <0700	May req inpatient stay Good discrimn in large groups of pts.

glucocorticoid hypersecretion (SAGH).The frequency of occurrence of this disorder varies between 1 and 29% depending on criteria used for its diagnosis.[6] Basal serum cortisol estimation at 9:00 AM is the screening test to rule out cushing's syndrome.Various tests for assessment of SAGH are 24 hours urinary free cortisol, midnight plasma cortisol, ACTH and high dose dexamethasone suppression test. However overnight 1 mg dexamethasone suppression test yields a diagnostic accuracy of 98% sensitivity and 80-98% specificity as per NIH consensus statement.[7] Plasma value of >138 nmol/l is associated with significant glucocorticoid autonomy. This should ofcourse be supplemented with one more diagnostic test for assessing hypercortisolism.

4. Androgen levels assessment: It is not a usual diagnostic work up for adrenal incidentaloma. Androgen overproduction is a hallmark of adrenal carcinomas, a low level of dehydroepiandrosterone sulfate is suggestive of adrenal adenoma.

Investigations

CT Scan: The CT scan of this patient is suggestive of an adrenal lesion of 3.4X2.4 cm. This lesion falls in the indeterminate category. The size is a determinant of malignant potential of an adrenal lesion.A lesion more than 3 cm carries a fairly high chances of being malignant.Most of the non-functional adrenal adenoma has an attenuation value less than 10 HU (Fig 1) with a specificity of 98%. [8] This patient has a value 24 HU which of course goes against lipid rich adrenal adenoma.There is still the possibility of lipid poor adrenal adenoma or pheochromocytoma. In any case be it a lipid rich or lipid poor adenoma the absolute wash out must be more than 60% which is not the case here. There is likelihood of pheochromocytoma which is supported by a CT finding of >10 HU and its characteristic of early enhancement and delayed washout. It is definitely going in favor of non-adenomatous lesions as well like adrenocortical carcinoma (ACCs), but most of the ACC are larger than 6 cm and has extension to surrounding structures and heterogenous appearance on CT. The possibility of non-adenomatous lesion is further reinforced by a wash out of only by 19% and early enhancement.Adenoma has an early enhancement and early washout >60% absolute and >40% relative washout. Other possibilities like myelolipoma, cyst, hemangioma, is less likely in view of CT finding having a HU >10 and a cyst does not enhance on contrast, and the wash out characteristics of rest of the lesions. The liver cyst is a benign one and spinal degenerative changes do not contribute to the adrenal lesion.

Plasma levels of catecholamines: Normal 24 hours catecholamine levels reduces the possibility of pheochromocytoma. Serum levels of catecholamines however is a better choice to rule out the diagnosis of pheochromocytoma. Pheochromocytoma may exist even when the catecholamine levels are normal.

Serum Cortisol: Basal Serum cortisol is falling within normal range, this principally rules out a endogenous hypercortisolism, however there can be possibility of sub-clinical autonomous glucocorticoidhy persecretion, this entity is devoid of clinical manifestations of Cushing's but has a higher value of cortisol. To rule out this particular entity there is hardly an agreement on the levels of serum cortisol and

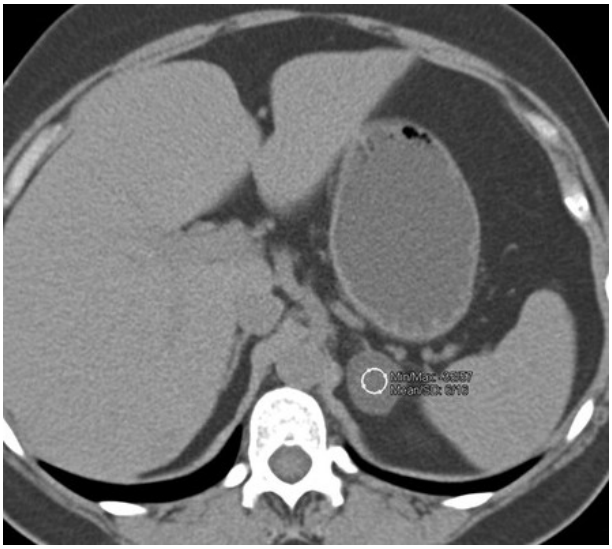


Fig 1 — Left adrenal mass with <10 HU attenuation consistent with non-functional adenoma. [Representative image only, not related to case]

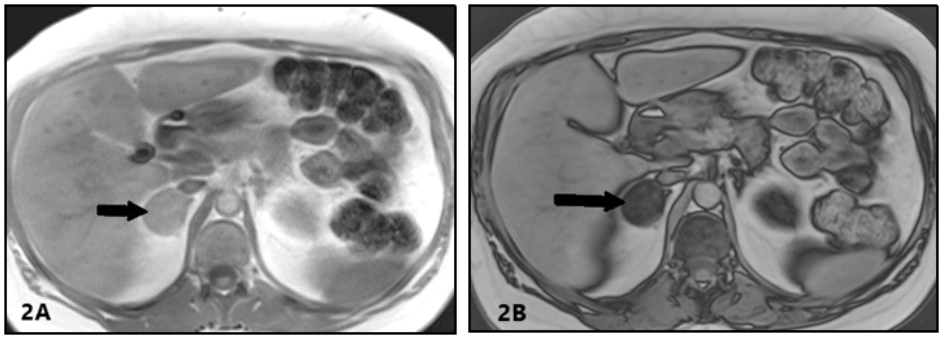
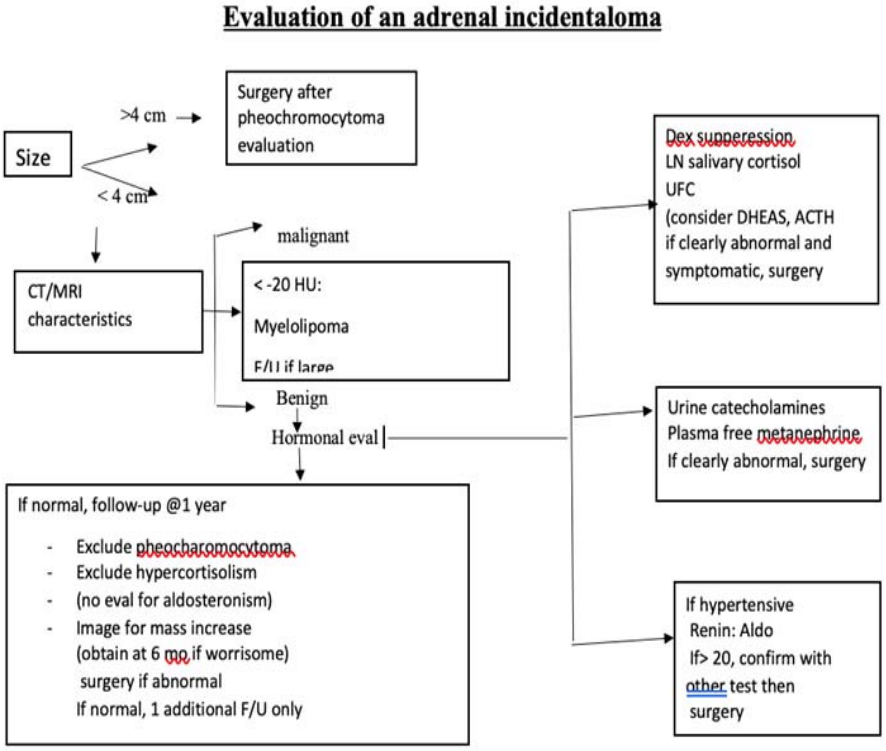


Fig 2 — MRI depicting loss of signal intensity in out of phase image (2B compared to 2A) owing to intracellular fat (Representative image only)

dexamethasone suppression test. The national institute of health has recommended 1 mg dexamethasone overnight test with conventional cutoff of 140 nmol/l.[9] However dexamethasone suppression test using 2 mg dexamethasone 6 hourly for 48 hours is used to exclude Cushing's especially in morbid obesity, alcoholism and diabetes mellitus.[10]Serum cortisol values as low as 50 nmol/l has been used to define sub clinical autonomous cortisol hypersecretion for both Cushing's syndrome and incidentaloma screening.[11] This patient has a 9 AM cortisol of 354 nmol/l and that suppressed adequately to low dose dexamethasone suppression test (LDDST) with a value of serum cortisol of 36nmol/l. The normal response to LDDST suggest a normal response and rules out the possibility of sub clinical autonomous cortisol hypersecretion.

Suggested evaluation of an incidentally found adrenal mass. Surgery for large masses with cause that requires resection, e.g. tuberculosis. LN, Late-night; Aldo, aldosterone; Dex, dexamethasone; F/U, follow-up; eval, evaluation; mo, months.



Q4. After Investigations how to relist the differential diagnosis ?

Relisting of Differential diagnosis: Will like to consider following Differential diagnosis.

1. Pheochromocytoma
2. Carcinoma
3. Metastatic lesion

Q5. What other investigations will help arriving at a diagnosis

Magnetic Resonance Imaging(MRI): MRI with chemical shift imaging (CSI) is the mainstay of evaluation of solid adrenal lesions. It utilizes the differential distribution of protons in fat and water as signals, the CSI signal loss can be measured quantitatively and qualitatively as well (Fig 2). The quantitative assessment is done as adrenal to spleen chemical shift ratio, by dividing the lesion to signal intensity ratios on the in-phaseimages (IP) by the out of phase images (OOP)[12]A. CSI ratio of less than 0.71 at 1.5 T field indicates a lipid rich adenoma. Alternatively adrenal signal intensity index is calculated as (IP-OOP signal intensity)/IP signal intensity X 100%, a measurement of greater than 16.5% at 1.5 T is consistent with a lipid rich adenoma. The sensitivity and specificity of CSI for differentiation of adrenal incidentaloma are reported at 81% to 100% and 94% to 100% respectively.[13] It is noteworthy that adrenal cortical carcinoma and pheochromocytoma demonstrate signal loss on OOP images.[14] ACC are generally heterogenous with areas of high signal intensity on T1 weighted and T2 weighted sequences. As the ACC arises from adrenal cortex hence it contains intracytoplasmic lipids and at times it is difficult to differentiate between adenoma and carcinoma especially when it is small .But otherwise differentiation can easily be done by a large size , heterogenous nature and spread to surrounding structures.

Pictorial CME

Cerebral Infarction following Head Injury

P R Sowmini[1], M Sathish Kumar[1], S Sakthivelayutham[1], K Malcolm Jeyaraj[1], R Viveka Saravanan[2], K Mugundhan[2]

Case 1 :

A 12 year old boy presented to usin an unconscious state following a road traffic accident. He regained consciousness the next day and was noted to have weakness of right upper limb and right lowerlimb. On examination, the patient was conscious, pupils 3 mm in size, equally reacting to light on bothsides and extra ocular movements were normal. Right upper motor neuron facial palsy was present. There was right upper and lower limb weakness of MRC grade 3 . Bilateral extensor plantarwas noted. Magnetic Resonance Imaging(MRI) brain showed T1 hypointensity, T2 & FLAIR hyperintensity with restricted diffusion in DWI and ADC map over bilateral basal ganglia suggestive of bilateral basal ganglionic infarcts (Fig 1). Magnetic Resonance Angiography (MRA) showed normal study. Routine blood investigations includingblood biochemistry, haematological profile,cardiac evaluation including echocardiogram were normal. Diagnosis of cerebral infarction following head injury was made. Patient was treated with antiedema measures, physiotherapy and supportive measures. Patient is improving.

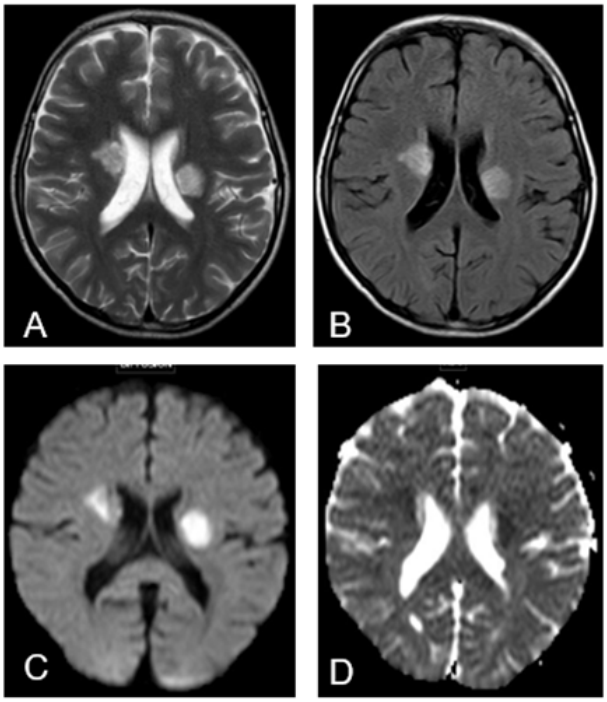


Fig 1 — MRI-T2 AXIAL (A) and FLAIR axial (B) images showing hyperintensity with restricted diffusion in DWI(C) and ADC (D) map over bilateral basal gangliasuggestive of acute infarct

Case 2 :

29 years old, previously healthy male was brought to the hospital in a state of unconsciousness following a road traffic accident. 3 days later, patient developed drooping of right eyelid. On examination, patient was consciousand had complete right third cranial nerve palsy with 5mm pupil size. There was no weakness of limbs. Plantars were flexor bilaterally. Magnetic Resonance Imaging(MRI)brain showed T1 hypointensity, T2 & FlAIR hyperintensity with restricted diffusion in DWI and ADC map over splenium of corpus callosum and right side thalamus suggestive of acute infarcts in splenium of corpus callosum and right thalamus

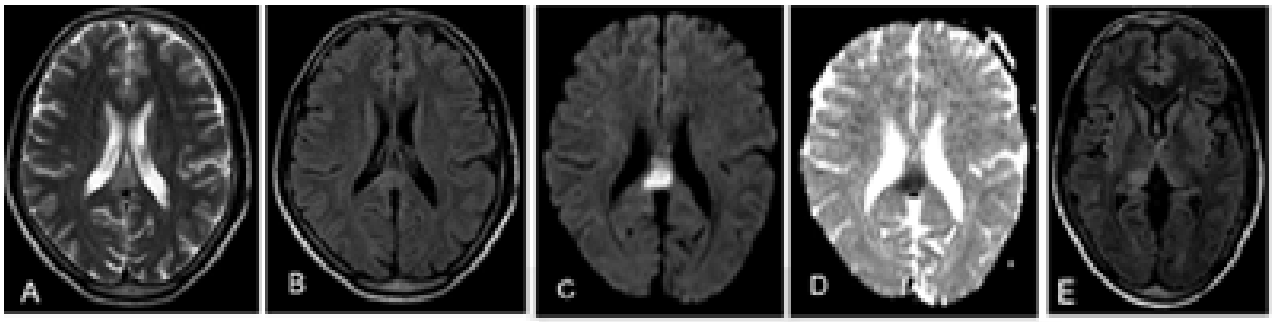


Fig 2 — MRI- T2 AXIAL (A) and FLAIR axial (B) images showing hyperintensity with restricted diffusion in DWI(C) and ADC (D) map over splenium of corpus callosum suggestive of acute infarct and MRI-FLAIR axial (E) shows hyperintensity in right thalamus

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(Fig 2). Magnetic Resonance Angiography (MRA) showed normal study. Routine blood investigations including blood biochemistry, haematological profile, cardiac evaluation including echocardiogram were normal. Diagnosis of

cerebral infarction following head injury was made. Patient was treated with antiedema measures, physiotherapy and supportive measures. Patient is improving.

Cerebral infarction following head injury occurs in less than 2 percent of all strokes. Other possible causes should always be excluded before making the diagnosis of post traumatic stroke. Imaging of brain and cerebral vessels must be done to look for lesions and dissection. Arterial dissection, thrombosis and vasospasm are the suggested pathogenic mechanisms of post traumatic infarcts[1]. Brain displacement across dural surface accounts for post traumatic infarction. Occipital infarctions are more common as posterior cerebral artery is being compressed by the temporal lobe against the tentorium.

Basal ganglia is supplied by lenticulate striate branches of middle cerebral artery. The angle between the middle cerebral artery and lenticulate striate artery is more acute and since these are functional end arteries, stretching and distortion of the angle of perforating branches during trauma leads to damage to the vessel and reduces blood flow. Less frequently, lenticulostriate,thalamoperforating and choroidal arteries are compressed against the skull base resulting in basal ganglionic infarction[2]. Corpus callosal infarcts are not common due to the rich blood supply from three arterial systems. Splenium is vulnerable than genu and body of corpus callosam.

The possible mechanismby which infarction occurred incase no 1 is due to distortionof lenticulostriate branches of MCA on both sides producing basal ganglionic infarcts and compression of right posterior cerebral artery in Case 2 causing right thalamic and splenial infarcts. The complete 3rd cranial nerve palsy on right side in Case 2 is due to ipsilateral paramedian thalamic infarct. The midbrain and thalamus have a similar vascular supply. Some individuals may have vascular variations also. Oculomotor nerve palsy is a common symptom of a midbrain infarction, but rare cases of a paramedian thalamic infarction causing third-nerve palsy without a definite lesion on the brainstem, have been reported. Even though there was no definite midbrain lesion in this case, the third nerve palsy can be partly attributable to the involvement of the oculomotor nuclei or fascicle, which is usually associated with thalamic lesion extension[3].

Conclusion :

Post traumatic infarctions are rare. They are closely related to anatomical peculiarities of brain skull base in children. Hospital admission, careful observation and early DWI MRI should be considered in patients having neurological deficits.

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History : Remembering the Stalwarts

Rudrajit Paul, Jyotirmoy Pal

Dr Sambhu Nath De (1915-1985) was an alumnus of Calcutta Medical College, whence he passed his M.B. in 1939 and DTMH in 1942. He started working as a demonstrator of Pathology in the same college. In 1947, he went to London to pursue a PhD course in Pathology. After returning, he remained in the same institution till his retirement in 1973.

Dr De was one of the foremost experts on the pathogenesis of Cholera in the world. His research publications garnered widespread citation. His monograph on cholera, "**Cholera: its pathology and pathogenesis**" Published by Oliver and Boyd, London, 1961 was once considered a seminal text by academics all over the world. Dr De was the first in the world to demonstrate that vibrio cholera secretes an enterotoxin and also demonstrated its mechanism of action.

Dr Sambhu Nath De

(This picture is in public domain in India)

Various eminent scientists all over the world, including Nobel Laureate Dr Joshua Lederberg have labelled his publications as "classic"s in the history of cholera and bacteriology research. Perhaps Dr De is the only medical scientist from India with noteworthy contribution in the global field of bacteriology in the last century.

Dr De never received any state or central government award or other recognition. He was nominated for Nobel prize twice but today, remains totally forgotten in his country. Unfortunately, there is not even a laboratory or a lecture theatre hall named after him in any medical college of Calcutta.

His most famous paper is cited below:

De SN — Enterotoxicity of bacteria-free culture filtrate of Vibrio cholerae. *Nature* 1959; 183: 1533-4

The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head.

— William Osler : 1914 Quote

Ads from the Past

Bi-Anicide : A treatment for Gonorrhoea

Rudrajit Paul

Before the discovery of penicillin and its derivatives, sexually transmitted diseases like gonorrhoea were virtually untreatable. People usually tried to hide the diseases due to social taboo and this led to quick spread of the infections.

Earlier, in the Nineteenth century, mercury or arsenic compounds were tried for STDs. Since these diseases were rampant in the aristocratic families of Europe, they spared no pains in procuring any possible cure for the disease. When news spread that a South American tree called Copaiba was effective in Gonorrohoea treatment, in 1859 Great Britain imported more than a 150 thousand pounds of the tree extract. Later, in the 1890s, some scientists even tried Gonorrhoea vaccine.

So, when sulphonamides were discovered, one of its first uses was for gonorrhoea treatment. This ad in JIMA, June, 1944 shows an early crude form of sulphonamide. It was effective. But later, as penicillin and cephalosporins were discovered, this fell into disuse. As the reader will see, in those days, the dose and direction for a tablet used to be written on the package. Thus, patients could buy them and use on their own.

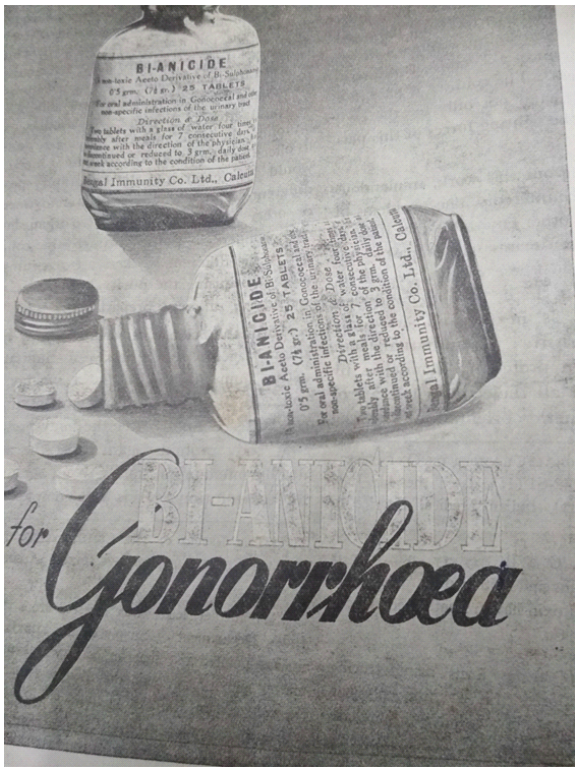

Fig 1 — The tablets for Gonorrhoea
Source : JIMA, June, 1944

Journey of COVID Warrior

The Psycho Social Ramifications of the COVID 19 — A Personal Treatise

Nandini Chatterjee[1]

The COVID 19 pandemic is taking its toll on humanity in more ways than readily discernable. The number of recoveries inspires hope but it needs to be ensured that apart from physical recovery a holistic rehabilitation of the sufferer is contemplated.

[*J Indian Med Assoc* 2020; **118(9):** 61-3]

Key words **: COVID 19, Holistic, Rehabilitation.**

The COVID 19 pandemic has revolutionized the way we look at disease and its consequences.. The pathology involves every organ system of the body – has immediate and far reaching sequelae.

But beyond medicine there lies immense psychological, social and economic implications whose enormity cannot be fully be gauged at present.(1)

However my own brush with the disease has triggered some reflections which I wish to share.

THE DENIAL :

The onset of fever is met with denial.

- I have been cautious enough.
- I have been meticulously devouring hydroxy chloroquine every week
- I work in a non COVID hospital.

THE ACCEPTANCE :

I go for the test when I fail to smell my favorite perfume.

I am COVID 19 positive. The information is to be digested; a brave front is to be put up as I feel my family is more vulnerable than I am.

THE DECISION :

Do I stay at home?
Do I stay at a Safe home?
Do I go to hospital?
Proper isolation is difficult at home.
Risk factors - looming in the background.
So the hospital it is.

"While healthcare service personnel are duty bound to serve without discrimination, the cooperation and support from society is a fundamental need for them to perform their duties with confidence,"

— Ministry of Health, Govt. of India

JIMA, Editorial, June, 2020

Editor's Comment :

- **It is natural to feel anxious, marginalized, fearful, and uncertain during and after COVID19 infection.**
- **A compassionate support system is necessary to deal with these issues comprehensively.**

THE DEPARTURE :

The family goes into quarantine.

The 102 ambulance arrives, - two PPE-clad individuals sitting at the front direct me over phone to open the door at the back and get into the vehicle.

I obey.

Curious onlookers on the lane stand and stare. I feel like a criminal being taken to jail.

I do not judge them- I see fear in their eyes.

THE HOSPITAL STAY :

I was febrile with a normal oxygen saturation.

But all around me were people on oxygen therapy, antibiotics, steroids, Remdisivir. So till I became a febrile five days later I was fearful and apprehensive.

I did not know whether I would have adverse effects from Favipiravir or LMWH which I received.

My being a medical professional has complicated matters. I am aware of the full spectrum of the disease.

THE SOCIAL MEDIA :

It is full of horror stories.

Documentation of recurrences, residual systemic damage, late complications and mortality – I am not ready to kick the bucket yet.

It is better not to enrich oneself too much via the 'whats app university'.

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Received on : 25/08/2020
Accepted on : 10/09/2020

THE APARTMENT NEIGHBOURS :

Panic stricken.

Demand sanitization (politely of course) of lift, common passages , our flat as well as our vehicle in the garage.

Is arranged by my family immediately, though expense for common areas is shared to be fair to them.

They ensure that my family is properly cooped up in the house.

THE CONVALESCENCE :

Fatigue- all consuming and improving at snail's pace.

The future- looks bleak. What does it hold in store for me?

THE REALIZATION :

This account will be incomplete if I do not acknowledge the help, good wishes, concern, empathy and encouragement I received from family, friends, colleagues, students, teachers, acquaintances, even my maids and driver.

I am overwhelmed and consider myself truly blessed.

I am filled with hope.

New drugs are coming up, vaccines are round the corner, the untiring endeavor of humanity to fight adversity continues- so all is not lost.

But what is very important is all sufferers of COVID19 may not be as privileged as I am, hence some discussion about this burning problem.

DISCUSSION :

Searching through literature to cope with my own insecurities – I find voluminous and thought provoking articles on the psychosocial impact of SARSCoV2 infection.

There are variable effects on the different sections of society like children, elderly subjects, health care workers, marginalized communities, known psychiatric patients apart from general adult population.[2]

The manifestations may range from panic, anxiety, obsessive behavior, hoarding, paranoia, depression even psychosis and post traumatic stress disorder (PTSD).[3] The most stressed, anxious, and depressed people are those who are in a relationship but not cohabiting, followed by single individuals. Those who have children show lower psychological impact, stress, anxiety, and depression than those with no children[4]

The so called 'infodemic' disseminated by the innumerable social media platforms seems to be aggravating these problems even more.[5]

Stigmatization, xenophobia, isolation, quarantine, loss of control over ones' life, financial insecurities , ill health and loneliness are the main factors that are leading to the psychological turmoil.[6,7]

In case of medical professionals are added feelings of vulnerability due to lack of definitive therapy and prevention, feelings of worthlessness and guilt, fear of infection, separation from family, overwork, assault from patient relatives – all resulting in early burnout phenomenon.[8]

‘ ؤتلµ نڑإ‘س ءے‘ارمی/و' .بالسیٔ س'ا/منرخٔ’

[Plague was dangerous, but quarantine was more dangerous : Rajendra Singh Bedi].

JIMA, Editorial, June, 2020

The WHO has released advisories to cope with the psychosocial epidemic which goes hand in hand with the viral pandemic. The 'm h GAP Humanitarian Intervention Guide' is a ready reckoner consult for health care workers to address mental health conditions.[9]

Untouchability — Other Face of Pandemic

JIMA, Editorial, June, 2020

The mainstay of management is an empathetic counseling support to patients and families, along with a healthy lifestyle modification advice involving diet plans, exercise and avoidance of substance dependence.[10-12]

CONCLUSION :

A comprehensive holistic approach is necessary to deal with this scourge. Apart from medical therapy, diet and lifestyle advice, counseling for morale boost up, and social rehabilitation should become part and parcel of COVID19 management.

"Unsung Heros of India's Corona War ......Write their history now".

Dr R V Ashokan

Hon Secretary General, IMA

JIMA, Editorial, June, 2020

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Journey of COVID Warrior

COVID-19 Impact on Health Care Workers

Surya Kant[1]

Novel Corona Virus causes COVID 19 (Corona Virus Disease of 2019) infection. In December 2019, SARS(Severe Acute Respiratory Syndrome) -CoV-2, was first recognized in Wuhan, China. Genetic sequencing of the virus suggests that SARS-CoV-2 is a beta –coronavirus; which is intimately linked to the SARS virus. Mostly patient develop mild or uncomplicated illness, but 14% often them leads to severe disease which needs hospitalization and oxygen therapy and among them 5% need intensive care.[1]. Health Care employees are at the frontline of this pandemic taking care of infected patients and thereby are at a greater risk of acquiring infection. Health workers impart a crucial job not only in the management of the sick, but also ensures adequacy of infection control and its prevention of infection. Systematic literature are scarce but available sources reflect an infection rate of 1% among health care workers (HCW's) with female preponderance. HCW's of all ages got infected but those with age greater than 55 years had high mortality after being infected. Case fatality rate among HCW's varied across the globe with 0.9% in China to almost 6.1% in India. Ignorance about the epidemiology and transmission of the disease, lack of protective gears due to epidemic unpreparedness were main attributable factors for infection in HCW's. This pandemic has shown great impact on mental health as well as on social wellbeing of health care workers. A proportion of the workforce are faced with depression(22.8%) ,insomnia(34.3%) and anxiety disorders(23.2%) leading to untoward consequences in few cases. Understanding COVID–19 infection and its impact on health workers is crucial not only for characterizing the transmission pattern of the virus but also as a means of prevention of the infection amongst the providers of health care who have a key role in saving the world from this pandemic.

[*J Indian Med Assoc* 2020; **118(9):** 64-9]

Key words **: COVID-19, Health care workers, Mortality.**

The ongoing epidemic, COVID-19 is devastating. Despite of the extensive accomplishment of control measures. The outbreak sparked in The city of Wuhan of, capital of Hubei province in China. The case fatality rate (CFR) has gradually incremented from 0.25 to 7%. It may also has the denominator consisting of asymptomatic cases which often remains hidden. The case fatality rate varies depending on age and presence of co-morbid conditions. Health care workers are one of the major vulnerable group as they deals with severe cases (likely with high viral load) and are in close proximity to the cases during procedures such as examination, handling of samples, surgical interventions, intubation and endoscopic procedures which can lead to the spread of virus.

Health care workers include not only doctors ,but all the staffs in the health care fraternity involved in dealing with a COVID–19 patients, including those who are present in the same place as the patient as well as those who may not have delivered direct care to the patients, but who, had indirect contact with the patient's body fluids, possible polluted items of environmental surfaces. This includes health care professionals , allied health workers and additional health workers such as cleaning and laundry personnel, X ray technician, clerks, nutritionists, social workers, laboratory personnel, cleaners, pharmacists, ambulance drivers, catering staff and many more.

According to WHO over 35000 HCW's have been infected with COVID 19 till April 28, 2020. The number is highly under-represented due to under-reporting and lack of systematic reporting of infections among healthcare workers to the WHO. Health care worker are being infected at work place and in the community. Hospitals have been the source of COVID 19 infection in almost every country including India.

Ancillary reports from China claim 3300 health care professionals have been infected and similarly 20% of health care workers from Italy have contracted the infection[4]. In a recently published article from China[5] it is reported that 110 out of 9684 Health care workers in tertiary care hospital positive for COVID 19 , With an infection rate of 1.1%. Majority (71.8%) of them were women with median age of 36.5 years. Most of

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Received on : 27/07/2020
Accepted on : 10/09/2020

them had non-severe disease (84.5%), while mortality was 0.9%. Major clinical scenario were: Pyrexia (60.9%), weakness (60%), dry cough (56.4%), sore throat (50.0%), and muscle pain (45.5%). Of them 15.5% were first-line HCWs whereas 1.4% were non–first-line HCWs. Nurses who were under the age of 45 years and not the first-line caregivers were at a greater risk to become infected than first-line doctors who aged more than 45 years, with an incident rate ratio of 16.1. Sub clinical infection prevalence is 0.74% among asymptomatic first line health care workers and 1.0% among non first line health care workers. Contact with index patients (59.1%), colleagues with infection (10.9%) and community-acquired infection (12.7%) are the main source of exposure in HCWs. Health care professionals who were not frontline workers were at a higher risk of infection during the early stage of the COVID 19 outbreak before protective measures were introduced. The mortality among Health care workers in various countries are shown in :Table1. The median age wise distribution of COVID-19 infection among HCW's are illustrated in Fig 1.

Another study was done in Netherlands[6] that involved 9,705 HCWs who were screened in two teaching hospitals in Breda and Tilburg. It identified 1,353 (13.9%) individuals who reported fever or other respiratory symptoms. Out of which, 6.4% workers tested positive for SARS Cov-2, representing 0.9% of all HCWs. But amongst those who were tested positive for COVID 19 only 3.5% had patient exposure. However, most of the HCWs had mild illness, with 93.0% satisfying the case definition of fever, cough, and/or shortness of breath. Median age of infection was 49 years, majority being women (82.6%).

Another study from China[7] where they screened orthopedic surgeons for COVID-19 and found 26 of them from 8 hospitals to be positive for Coronavirus. The suspected places of exposure were general wards (79.2%), public places at the hospital (20.8%), operating rooms (12.5%), intensive care unit (4.2%), and outpatient clinic (4.2%). There was transmission from these doctors to others in 25% of cases included family members, colleagues, patients and to friends. Avoidance of wearing an N95 respirator and severe fatigue was found to be risk factors whereas wearing respirators or masks all of the time was found to be protective measures.

Among physicians affected by COVID-19, general physicians constitute the bulk of the burden. Specialty wise affected physicians are depicted in Table 2 and Fig 2.

Although exact data on the burden of COVID-19 infection among HCW's in India is not available, a reputed national daily reported that according to Indian Medical Association, more than 1955 doctors were infected till 31st August , 2020. Out of 1955, 890 belong to general practitioners, 767 resident doctors and 296 house surgeons (depicted in Fig 4) ofthem 266 died due to Covid-19 until last data was compiled as on 31st August 2020. India's first female cardiologist Dr. S Padmavati died at age of 103, due to COVID 19 on 29th August 2020. She was founder

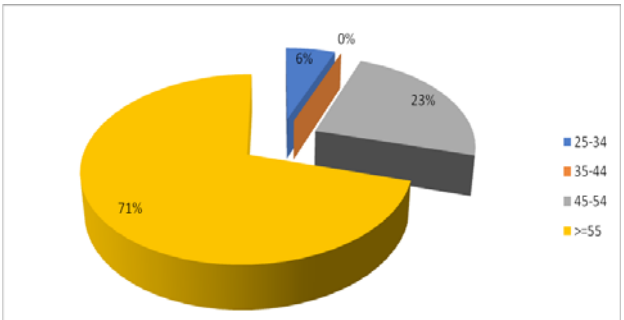

Fig 1 — Pie Diagram showing Distribution of median age at death due to COVID-19 among physicians across the world

Table 1 — *Mortality among health care workers in various countries were as follows*[9]

Country	Frequency (%)	Median Age(years)
Italy	79(39.9%)	69
Iran	43(21.7%)	54
China	16(8.1%)	51
Phillipinnes	14(7.1%)	62
USA	9(4.6%)	67
Indonesia	7(3.5%)	58
France	6(3.0%)	67
Spain	6(3.0%)	59
United Kingdom	4(2.0%)	66
Brazil	2(1.0%)	53
Mexico	2(1.0%)	45
Turkey	2(1.0%)	67
Canada	1(0.5%)	62
Egypt	1(0.5%)	50
Greece	1(0.5%)	-
Honduras	1(0.5%)	56
Pakistan	1(0.5%)	26
Poland	1(0.5%)	-
Serbia	1(0.5%)	59
South Korea	1(0.5%)	60

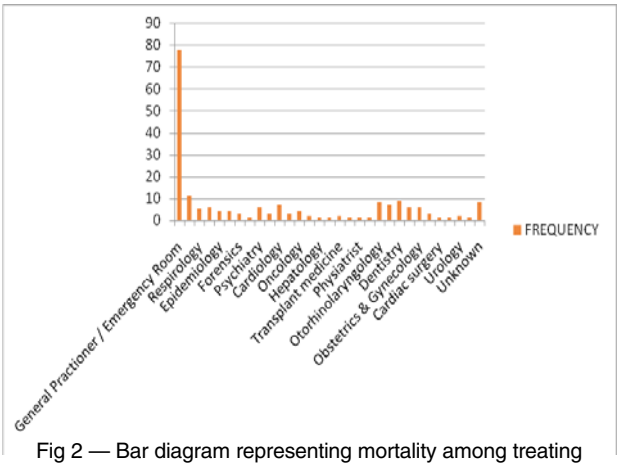

Fig 2 — Bar diagram representing mortality among treating physicians due to COVID-19 according to Speciality[9]

of National Heart Institute, Delhi. She was famous as god mother of Cardiology. State wise distribution of COVID-19 infected HCW's and mortality due to it in India have been depicted in figure-3 and 5 respectively. Over all till 31st August 2020 more than 87000 health care workers have become infected out of them 573 were died.

The deaths noted in less than 40 years are 21 per cent, below 50 years are 29.6 per cent and below 60 years are 55.5 per cent.Age wise distribution of mortality among HCW's in India have been depicted in figure-6.In Indian scenario the highest risk has been seen in operation theatres. The case fatality rate among doctors affected by SARS-Cov-2 was 6.1. A comparison of case fatality rate among general population and HCW's has been represented in Fig 7. High viral load, with physical and mental fatigue of fighting the infection, inadequate supply of PPE during the initial stages of the pandemic , gaps in following precautions and misinterpreting the seriousness of the illness are some of the factors which are implicated in the Indian context ,for mortality and morbidity of HCW's associated with COVID-19 in India[8].

Due to inadequacy of personal protective equipment and long hours of works, the risk of infection got incremented in health care workers across the globe which includes India also.

When healthcare workers get sick, they either go into quarantine or get admitted to the hospital. The total number of healthcare workers and hospital beds are limited. The system gets stressed because of less number remaining workers taking on greater volume of workload. Work burden mainly includes sick health care worker and patients. This increases the infection risk of among the remaining healthcare workers, giving rise to a vicious cycle. Hospitals might also get shut, if there is increased number of infection in HCW's, increasing the stress in the overall system. Healthcare workers cannot be replaced easily. It is not easy to train a new worker in order to perform the same task. Most of these infections were transmitted by patients in a hospital environment which led to temporary closure of certain healthcare facilities. In Maharashtra 42% doctors, 70% nurses almost 80% auxiliary medical workers gets coronavirus infection. Close to 10 hospitals in Maharashtra had to be completely or partially shut down as a consequence of exposure to Covid-19. Other states also had similar reports.

Tributes to healthcare workers are pouring in from around the world amid the COVID-19 pandemic, as the world gives medical heroes a standing ovation from windows and balconies. Blowing of Conch shells, ringing bells and cheering to show solidarity with the Heath Care Workers for their laudable work to battle COVID-19 was done all around India while on the other side there has also been reports of Physical Violence against doctors and nurses in parts of the same country.....

..... When the fear of infections is high among doctors, the public too will be scared and this is the new pandemic.

JIMA, Editorial, June, 2020

The extent of local spread was underestimated previously in countries like Spain, UK and USA which resulted in setting a vicious cycle of healthcare workers getting infected and transmitting it on to there colleagues and patients. If sources are to be believed, in Italy, doctors died due to lack of knowledge about the local spread of the disease. They were treating these patients as annual flu infections which turned out to be COVID 19. In Spain, doctors were not priorly informed about the extent of spread, hence they did not take any possible precautions. Most of the infections among the HCW's occurred in the early phase of the disease when ignorance about the disease transmission and protective equipments – both were at the nadir point. Among all risk factors, ignorance was the most

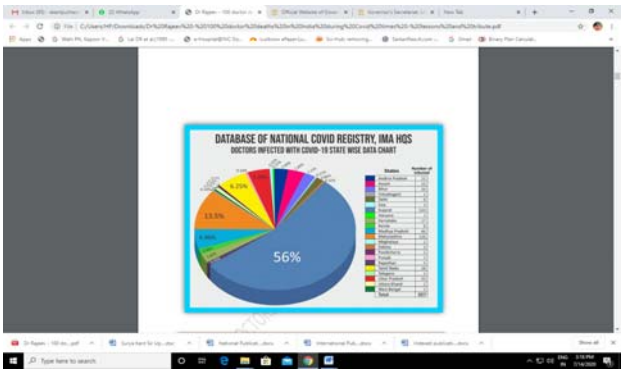

Fig 3 — Pie Diagram representing state wise distribution of COVID-19 infected HCW's in India[15]

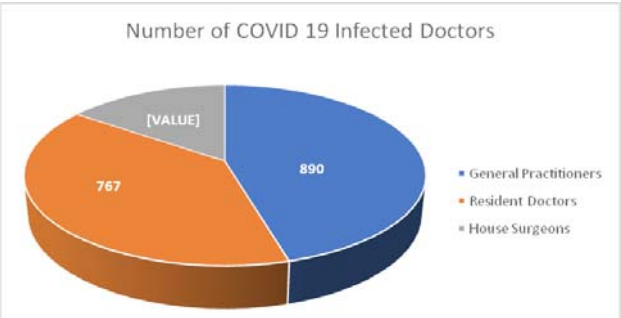

Fig 4 — Pie Diagram representing Number of COVID 19 Infected Doctors[8]

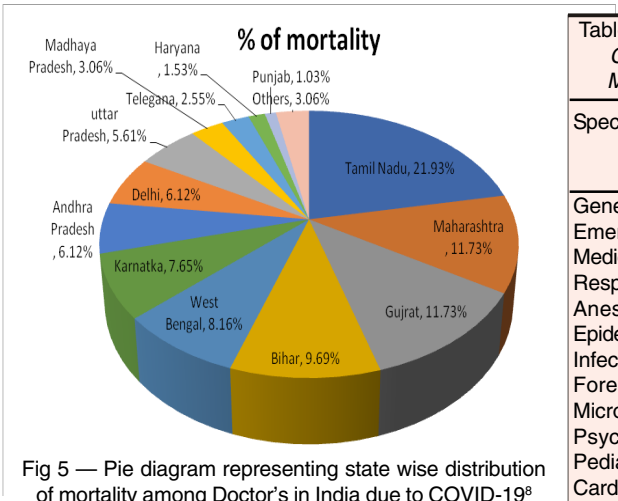

Fig 5 — Pie diagram representing state wise distribution of mortality among Doctor's in India due to COVID-19[8]

dangerous, as well as the most remediable one. Not taking the necessary precautions from the very beginning leading to massive transmission among the care providers.

There is no data available regarding infection rate in auxillary health workers, like field workers, ward boys, sanitation workers, security guards, lab attendants, peons, laundry and kitchen staff.

Medical staffs are being prioritised in many countries, but shortage of PPE are one of the major drawback in most affected facilities.

Cluster of the infections among HCW's occurred at the initial stages of the pandemic due to unpreparedness and lack of protective gears. Alongside their personal safety, HCW's are more concerned, about passing the infection to their families.

In view of this pandemic, health care workers are in direct contact with the cases and are instrumental in the diagnosis, treatment, and care of COVID -19 patients. They are at a high menaceof developing psychological distress and other mental issues .Decisions have to be made fast, with efficient triaging and isolating suspects, in deciding whether to shut down departments and in operation theatres when a patient or staff is tested positive, whilst on limited resources. The continuously growing number of COVID-19 cases, prodigious workload, shortage of personal protection equipment, extensivemedia coverage, lack of specific drugs and feelings of beingun supported may all contribute to the mental burden of mental health diseases of these HCW's. The pressure to act on time and to be appropriate during these critical situations has an increasing effect on the mental health[10]. The use of protective equipment continuously for longer periods causes difficulty in breathing and limited access to toilet and water, resulting in subsequent physical and mental stress. A recent study among healthcare professionals at a tertiary infectious disease hospital for COVID-19 in China, discovered a high incidence of anxiety and stress disorders among health care staff on the forefront ,involved in active management of patients[11]. The study showed that

Table 2 — *Reported Physician Deaths from COVID-19 by Practice Specialty and Median Age (n=198) on April 5, 2020*[9]

Speciality	Frequency (%)	Median Age (years)
General Practitioner(GP)/ Emergency Room	78 (40.6%)	67
Medicine	11 (5.8%)	70
Respiratory Medicine	5 (2.6%)	70
Anesthesiology	6 (3.1%)	68
Epidemiology	4 (2.1%)	66
Infectious Disease	4 (2.1%)	64
Forensics	3 (1.6%)	65
Microbiology	1 (0.5%)	-
Psychiatry	6 (3.1%)	64
Pediatrics	3 (1.6%)	64
Cardiology	7 (3.7%)	68
Hematology	3 (1.6%)	63
Oncology	4 (2.1%)	46
Neurology	2 (1.6%)	34
Hepatology	1 (0.5%)	69
Gastroenterology	1 (0.5%)	29
Transplant medicine	2 (1.0%)	60
Radiology	1 (0.5%)	43
Physiatrist	1 (0.5%)	68
Occupational Therapy	1 (0.5%)	61
Otorhinolaryngology	8 (4.2%)	61
Ophthalmology	7 (3.7%)	57
Dentistry	9 (4.7%)	71
General surgery	6 (3.1%)	63
Obstetrics & Gynecology	6 (3.1%)	59
Neurosurgery	3 (1.6%)	70
Cardiac surgery	1 (0.5%)	-
Orthopedics	1 (0.5%)	54
Urology	2 (1.0%)	66
Plastic surgery	1 (0.5%)	62
Unknown	8 (4.0%)	

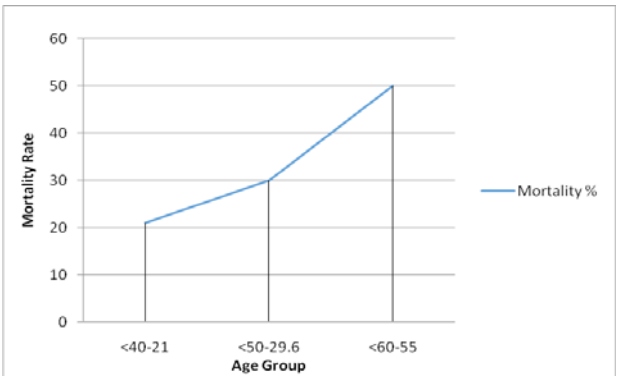

Fig 6 — Age wise distribution of mortality among HCW's in India[8]

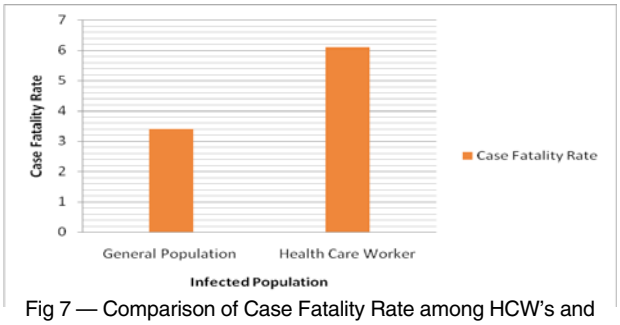

Fig 7 — Comparison of Case Fatality Rate among HCW's and General Population

nurses have a higher incidence of anxiety than doctors. Another study[12] revealed a significant relationship between the prevalence of physical symptoms and psychological outcomes among healthcare workers during the COVID-19 outbreak. A recently published meta-analysis showed a pooled prevalence of Anxiety (23.2),Depression (22.8%) and Insomnia (34.32%) as the three most commonly encountered psychiatric problems among HCW's working in COVID hospitals. Further scrutiny showed gender and occupational differences .Female staff showed higher incidence of affective disorders as compared to male their male colleagues[13]. In India ,also the psychological burden of Covid19 has been alarming. Till April 15th , four healthcare workers died in road traffic accident due to mental and physical stress of infection. Five nurses and one doctor committed suicide because of the stress and stigma of contracting COVID-19 .

Health-care facilities, globally are operating at more than maximum capacity for many months till date. But health-care workers are not inanimate like ventilators or wards, they cannot be urgently manufactured or run at maximum effectiveness for longer duration. It is vital for the administration to look upon health care workers not simply as mechanics , but as human individuals. In this global crisis HCW's are the most essential link in the chain of prevention and control of this pandemic. Therefore ,their safety should be given maximum priority . Provides PPE and cancel unnecessary events there should be prioritization of resources, food rest and family support. Infections among the health workers can be prevented by using proper personal protective equipment and by undertaking taking proper administrative, academic and engineering preventive methods. Presently, health-care workers are every country's most precious resource[14].

Clinicians may not have complete control over situation, but we have to rise to perform our duties and service with equanimity. COVID 19 have exposed ugly fracture of our society, not only in terms of infrastructure and policy also attitude of society perhaps carrying the virus in latent phase. Pandemic only revitalized the virus from latent to dormant phase.

JIMA, Editorial, June, 2020

Amidst all this, it is essential that HCW's also take care of their physical, mental and social wellbeing so that they can discharge their duties to their utmost ability. To overcome the stress and fatigue, some lifestyle modifications can be followed. It is essential to follow a daily routine with adequate sleep (6-8 hrs) and healthy diet. Drinking lukewarm water, concoction and herbal tea may also prove beneficial. Regular exercise and Pranayama have proven benefit in boosting the immunity. Connecting with one's hobby in leisure time can ease out the mental stress. It is always encouraged to talk openly with family or peers , in case one feels any kind of pressure. Engaging in spiritual activities can also boost ones confidence and give strength to overcome this adversity.

Conclusion

The few studies that we have so far in this regard has shown us that the spread of COVID-19 amongst health care workers was basically due to unpreparedness because the nature of the devil attacking us was not well known and studied . The rate of infection was nearly 1% among HCW's. Females were more commonly involved as majority of the workforce of our healthcare workers consists of women. The mortality ranges from 0.9% to 11% in different countries. HCW's of all ages got infected, however the mortality was higher in those above 55 years of age.

Doctors of all medical and surgical faculties can get infected. Falling incidence of Nosocomial COVID-19 infection suggests effective control measures that should be increase response to the promptly sprouting epidemic in order to provide utmost protection to our HCWs and suffering patients.

The spread of the pandemic was not the cause of exhaustion of health facilities rather it exposed the existing lacunae in the health services across the globe. As it is said , *The Dead teaches the living* ,it is after the brave sacrifices of so many health workers who lost their lives treating the diseased that the government and health systems realized that the health workers are the most important resource in this pandemic and started taking adequate measures to protect it. As doctors we felt there was this implicit rule that we must be above sentiments, above agony, above breakdown – until difficult times came that challenged these concepts. We all have challenging times, but doctors and health care providers must believe that they should be capable enough to get over these feelings rapidly in order to be there for their patients and their miseries. If in coming times no further solutions or treatments are possible, health care workers should deliver ease and steadiness for patients and their families. This is a moral calling, one that we cherish deeply. Now health care worker will become more sensitive to the soreness of patients as they themselves cannot frequently see their loved ones, their own fear of getting infected with

COVID-19, and transmitting the infection to their families will further challenge there potential to work with maximal efficacy. All of these fears can become devastating with this growing pandemic. Health care worker therefore, should function and tolerate pain as human heroes. These are extremely hard times and HCW's are indeed heroes- heroes in human skin with human sentiments that must beaccredited and sheltered.

THROUGH THIS ARTICLE WE WOULD LIKE TO PAY TRIBUTE TO ALL THOSE HEALTH CARE WORKERS WHO HAVE LAID DOWN THEIR LIVES FIGHTING COVID-19 AT THE FRONTLINE.

Though dusk is advancing as a lazy surprise
All musics have paused with signs divine
Though I have no companions in vast skies
Though fatigue is creeping in my chassis
Doubts are reverberating in silent paean.
All horizons are covered with obscurities
Still O' my bird , O' bird of mine's
Do not fold your wings , do not close eyes.

Dussamay - Rabindranath Tagore

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Drug Corner

Consensus Statement on : Favipiravir as an Empirical Therapy for Influenza-like Illness during COVID-19 Pandemic

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The COVID-19 pandemic continues to have a serious impact on the lives of millions of people worldwide. Empirical therapy is being used to reduce morbidity and mortality of COVID-19 patients. Favipiravir, which is an oral broad-spectrum anti-viral agent with proven efficacy against various RNA viruses, acceptable tolerability profile and favorable benefit-risk ratio in short term use, has got an emergency use authorization in many countries including India for the treatment of mild to moderate cases of COVID-19. It has demonstrated promising results in terms of rapid viral clearance, quick symptom control, and pulmonary radiographic improvement. Due to reasons such as lockdown, isolation, diagnostic delays, fear of quarantine or getting tested, cost, etc., the golden time period (first 24-48 hrs) is lost in COVID-19 patients which is crucial for initiating antiviral therapy. Therefore, the panel members of *'Academy of Advanced Medical Education'* propose that favipiravir can be recommended in confirmed, early probable and possible cases of mild and moderate severity as an empirical therapy during current pandemic. It is important to counsel the patients and explain to them about the limited clinical evidences with favipiravir, therefore, a signed consent form from patient must be kept before initiating treatment. Well-designed double-blind controlled trials are urgently required to understand this further.

[*J Indian Med Assoc* 2020; **118(9):** 70-6]

Key words **: COVID-19, Favipiravir, SARS Cov-2, Pandemic, Anti-viral.**

Introduction & Epidemiology :

COVID-19 pandemic has affected more than 29.50 million people worldwide, more than 4.94 million people in India and the number is going up daily. Mortality in COVID-19 is also climbing rapidly, in India alone nearly 81,000 have died.[2] Older adults and people of any age who have comorbidities namely hypertension and

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Received on : 04/09/2020
Accepted on : 12/09/2020

Editor's Comment :

- **There is no definitive therapy against COVID-19, therefore, empirical therapy with repurposed antiviral agents are being used in an attempt to reduce morbidity and mortality in COVID-19 patients.**
- **On 20 June 2020, favipiravir, was approved with 'restricted emergency use authorization' by the DCGI in India for mild to moderate cases of COVID-19.**
- **Due to variety of patient related, diagnostic and operational challenges, the golden time i.e. the first 24 to 48 hours are lost which are crucial for initiating antiviral therapy. Favipiravir, being a broad-spectrum anti-viral agent with promising results and mild/ manageable side effect profile in mild to moderate cases of COVID-19 patients, can be used empirically in confirmed, early probable and possible cases during pandemic period for rapid viral clearance, quick symptom control, and pulmonary radiographic improvement.**

diabetes, have shown severe disease and worse prognosis. As of today, there is no vaccine available for COVID-19 nor there is any definite drug therapy. Therefore, many older molecules are being studied vigorously. A various group of drugs including broad spectrum antivirals, antimalarials, antibiotics, anti-helminth, vaccines like BCG, MMR as immuno-modulators, minerals, vitamins, anti-inflammatory, etc. are being employed as experimental adjuncts to supportive care against COVID-19.[3]

Phases of COVID-19 Infection :

It has been proposed that COVID-19 infection in the lungs includes three important phases:

1. An initial phase encompassing viral replication and relatively mild symptoms; also called the "early infection phase".

2. A second phase, which is characterized by adaptive immunity stimulation and predominance of respiratory symptoms; also called the "pulmonary phase".

3. And, in few cases, a third and the last phase with progress to a hyperinflammatory condition; also known as the "hyper inflammation phase".

Per the infection phase, clinical features range from mild symptoms (fever, cough, myalgia or fatigue, sore throat, headache) to acute respiratory distress syndrome (hypoxemia, shortness of breath) to ARDS, shock, multi-organ failure respectively.4Many Indian pulmonologists, especially from our expert group, reported that there is a 4th phase, the "Recovery phase with/without Fibrosis" or post-discharge phase of prolonged symptoms of residual hypoxia and shortness of breath which they are seeing in many of their Indian patients who need to be on prolonged oxygen therapy, steroids and even antifibrotics.

Case Definitions of COVID-19[5]— *(Based on clinical, epidemiological and laboratory parameters)*

• Possible Case

■ A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR,

■ A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR,

■ A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

• Probable Case

■ A possible case for whom testing for the COVID-19 virus is inconclusive. OR,

■ A possible case for whom testing could not be performed for any reason

• Confirmed Case

A person with laboratory (RT PCR or Rapid Antigen Tests) confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Clinical Severity & Assessment Parameters of COVID-19[6] :

(Clinical Management Protocol: Covid-19 Version 5 03.07.20 Government of India Ministry of Health and Family Welfare Directorate General of Health Services)

• Mild

Patients with uncomplicated upper respiratory tract infection may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, and headache with no evidence of breathlessness or Hypoxia (normal saturation).

• Moderate

Patients with pneumonia with no signs of severe disease but with the presence of clinical features of dyspnoea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute.

• Severe

Patients with Severe Pneumonia, Acute Respiratory Distress Syndrome, Sepsis, and Septic shock. Clinical parameters include clinical signs of Pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air.

Unmet Need: An Outpatient Treatment that Helps Prevent Hospitalization :

Early Outpatient Management of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis:

Based on various studies that addressed the treatment of mildly symptomatic high risk COVID -19 patients, investigators have suggested that there is a compelling argument for early outpatient treatment of symptomatic, high-Risk Covid-19 patients that should be ramped-up immediately as a key to the pandemic crisis.[7]

Early Intervention Initiation in High-Risk COVID-19 Patients :

Owing to the understanding that disease progression can occur quickly in stable patients and that viral loads are the highest early in the infection course, and hence rapid initiation of therapy in high-risk populations (patients who are hospitalized or outpatients who are at high risk of complications) is rational and should be considered.[8]

Early intervention is vital to halt the fatal pulmonary immunopathology. Thus, it is strongly recommended that the current treatment guideline be modified to initiate treatment very early in COVID-19 patients. This may be particularly crucial for high-risk patients.[9]

While there are weak or no pieces of evidence for benefits of drugs like hydroxychloroquine and lopinavir-ritonavir, few drugs like favipiravir, dexamethasone, and remdesivir were found to be effective in the management of COVID-19.[10]

Early Intervention Initiation to Diminish Virus Replication and Improve Outcomes:

Over 80% of COVID-19 patients have mild disease. The clinical improvement rates at 7 days with Favipiravir were 73.8%, 66.6% and 40.1% for mild, moderate and severe disease, in that order.[11]

The phase 3 SIMPLE II trial in patients with moderate COVID-19 disease showed that 5 days of remdesivir treatment was 65% more likely to yield clinical improvement at day 11 than the standard of care (P = 0.18). These data show that early intervention with a 5-day treatment course can significantly improve outcomes.[12]

Indian Favipiravir Clinical Trial demonstrated 40% faster accomplishment of "clinical cure" in the Favipiravir treatment arm (3 days), compared to the control arm (5 days) (p=0.029). 69.8% of patients in the Favipiravir treatment group achieved clinical cure by Day 4, which was statistically significant in comparison to 44.9% observed in the control group (p=0.019).[13]

Expert Group Opinion and Recommendations:

A panel of senior respiratory physicians and pulmonologists having vast experience in the management of COVID-19 was constituted by 'Academy of Advanced Medical Education' for developing the consensus statement and recommendations regarding the use of favipiravir in mild to moderate cases of Covid-19 as an attempt to guide the medical fraternity.

"Owing to its overall acceptable tolerability profile and favorable benefit-risk ratio in short term use, Favipiravir can be recommended in confirmed, early probable and possible cases of mild and moderate severity as empirical therapy. The Expert Group further opined that some of the tests such as LDH, D-dimer, CRP, CBC (especially Neutrophils/Lymphocytes Ratio), serum Ferritin should be suggestive of COVID-19. CT scan findings could serve as a significant diagnostic tool as it has the advantage of quick turn over time & is widely available.

There could be strong clinical suspicion of Covid-19 infection despite of negative RTPCR. In our country, there are times when testing is not done for operational reasons or it may be false negative - pending confirmation. There could be sampling or processing errors in laboratories. Real Time PCR at many places is done by appointment and it may take up to 3 days for reports to be available.

Per the Expert Group, empirical Favipiravir therapy should be initiated within 24 to 48 hours as the drug is mainly effective in initial phase (it acts on the viral replication). It is recommended that all possible tests like basic biochemistry including liver and renal function test, tests for inflammatory markers &x-ray chest / CT scan/ HRCT chest must be done as per the facility before the initiation of Favipiravir therapy. One may have to investigate further depending on associated co-morbidities.

Additionally, the Expert Group proposed (no published evidence) that any acute febrile illness suggestive of COVID-19 should be treated as COVID-19 in this pandemic situation unless proved otherwise. When used empirically, if the diagnosis is proved otherwise, the treatment may be discontinued."

The expert group strongly feels that robust double-blind control studies involving a larger group of patients are required to understand this further. Nevertheless, with the available clinical evidence and the panel's

expertise, the expert group believes that if Favipiravir is used early in the course of the disease, it may be able to bring about early improvement and may help reduce hospitalizations and prevent complications. Clinical judgment may be taken on a case-to-case basis. When used empirically, if the diagnosis is proved otherwise, treatment could be discontinued. For diagnosis, if the Rapid Antigen Test is positive, the patient is categorized as a confirmed case. Probable cases with a negative Rapid Antigen Test should undergo RT-PCR tests and these cases should be offered Favipiravir treatment option. RT PCR can be false negative is up to 30% cases and treatment may not be stopped in such cases if the clinical suspicion and the ancillary diagnostic tests are suggestive of SARS Cov2 infection (i.e probable case). Approach to continuation of favipiravir treatment in such cases should be defined by the clinical judgement of the treating physician. It is crucial to counsel the patient and explain to them about the limited clinical evidence and get a consent form signed from patient before starting the treatment with favipiravir. Also, this drug Favipiravir should be available as soon as possible in all retail medicine stores to be dispensed with a prescription of authorized medical practitioner for the early institution of treatment.

The expert panel was also in the opinion that moderate to severe cases with rapidly worsening situation should be evaluated further to start another antiviral agent Remdesivir. Remdesivir is an injectable drug and has received 'restricted emergency use authorization' by DCGI in India for the management of patients with severe COVID-19 infection only.[14]

Favipiravir Mechanism of Action :

Favipiravir is a derivate of pyrazine carboxamide. Its chemical name is 6-fluoro-3-hydroxy- 2-pyrazinecarboxamide. It works via inhibition of viral RNA dependent RNA polymerase (RdRp). Favipiravir is approved for novel epidemic influenza strains that do not respond to standard antiviral therapies in Japan. As a purine analogue, it functions as a chain terminator at the site of incorporation of the viral RNA and decreases the viral load. Favipiravir ends elongation after the incorporation of a single favipiravir molecule and after the incorporation of two consecutive favipiravir molecules, and the synthesis of this complementary viral RNA strand cannot be finished. Favipiravir treatment increases the frequency of transition and transversion in viral genomes, and these mutations are hypothesized to be caused by favipiravir, resulting in lethal mutagenesis. Among antiviral drugs, one distinctive feature of favipiravir is its broad-spectrum activity toward RNA viruses, comprising influenza virus, rhinovirus, poliovirus, ebola and respiratory syncytial virus.[15]

Safety/ Adverse Reactions[16]:

The most common adverse drug reaction with favipiravir include mild to moderate diarrhea, an asymptomatic increase of blood uric acid and hepatic transaminases, and a decrease in the neutrophil counts.

Contraindications, Warnings & Precautions[16]:

Favipiravir is contraindicated in patients having severe renal, hepatic impairment, and during pregnancy and lactation. It is also contraindicated in those having hypersensitivity to the active substance or any of its excipients. It is advised to the female patients of childbearing age that they rule out pregnancy before starting therapy with favipiravir. Adults are advised to use the most effective contraceptive methods, for up to 7 days, post the completion of the treatment. Instruct the male undergoing treatment to refrain from sexual intercourse with a pregnant woman. Patients with a history of abnormalities in the metabolism of uric acid or having gout should be cautious as blood uric acid level may increase, and symptoms may get aggravated with favipiravir use. Although the causal relationship has not been established yet, psychoneurotic symptoms such as abnormal behavior after administration of anti-influenza drugs like Favipiravir have been reported.

Use in Special Populations[16]:

- *Pregnancy & Lactation*: Favipiravir is contraindicated in pregnant women due to its teratogenic potential and embryotoxicity in animals. It is also contraindicated in lactating mothers.
- *Pediatric*: Favipiravir has not been approved in children.
- *Elderly*: Should be administered with care by monitoring their general conditions.
- *Liver function*: An increase of plasma level of Favipiravir has been reported with liver impairment and it may transiently increase hepatic transaminases.
- *Renal impairment*: Not studied in trials.
- Use with care in mild to moderate hepatic and renal impairment.

Dosage[16] :

The approved dosage of favipiravir in India for adults is 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily from 2nd day onwards and

based on clinical evaluation, it can be given up to a maximum of 14 days.

International Status :

Favipiravir was primarily used for the treatment of Influenza and was developed by Toyoma Chemicals in Japan. The drug has shown positive results in terms of reducing treatment duration and improved lung conditions in Covid-19 patients.

COVID-19 therapeutic management guidelines include Favipiravir in Russia, Japan, UAE & Saudi Arabia and it is currently being used for mild to moderate cases of COVID-19 and has a dosage duration of up to 14 days based on the condition of the patient. Approximately 18 global CTs are ongoing with favipiravir in more than 3000 subjects in clinical trials globally including India, USA, Canada, Italy, China, France, UK, and other countries. It has been approved by Italy & China for experimental use/ compassionate use in COVID-19.

Indian Status :

Favipiravir has been approved with restricted emergency use authorization by DCGI in India for mild to moderate COVID-19 management. Treating physician or prescriber needs to get a consent form signed from patient before starting the treatment with favipiravir.[14]

Favipiravir in Co-morbid Patients :

Data from the Japanese registry regarding the clinical use of Favipiravir in COVID-19 which included a total of 2,158 patients across 407 hospitals had about 49% of comorbid patients (including diabetes, hypertension) and 52% aged above 60 years. The study results demonstrated clinical improvement in 84.5% and 87.8% patients with Favipiravir in moderate and mild COVID-19 patients respectively at the 14thday.[17]

Evidence from Clinical Trials Globally :

• **Favipiravir vs Lopinavir/ Ritonavir —** An open-label, double arm, non-randomized study was conducted wherein patients who tested positive for the novel coronavirus RNA either received Favipiravir or Lopinavir/Ritonavir. In the Favipiravir (FPV) Arm (n=35), the patients received 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14 while those in the comparator arm (n=45) received Lopinavir (LPV) 400 mg/ritonavir (RTV) 100 mg twice daily. In addition, all participants received IFN-a1b 60 mg twice daily by aerosol inhalation. The endpoints of the study consisted of comparison of the time of viral clearance, and the improvement rate of chest computed tomography (CT) scans on Day 14, after treatment and safety assessment. The median time of viral clearance for the patients managed with FPV was 4 days which was significantly lower than LPV/RTV patients (11 days). Patients on FPV demonstrated greater improvement in chest CT after treatment (at day 14) compared to another arm (91.4% versus 62.2 %).The total adverse events in the FPV arm was four (11.43%), which was significantly lesser than those in the comparator arm (55.56%).[18]

• **Favipiravir vs Umifenovir —** A prospective, multi-centric, comparative trial, consisting of 240 patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older was conducted. The patients were randomly assigned to receive either the conventional therapy plus Favipiravir or control (Umifenovir) drug. The primary outcome considered was clinical recovery rate at day[7]. Duration of fever, cough relief latency, and auxiliary oxygen therapy or non-invasive mechanical ventilation rate were considered as the secondary outcomes. A total of 120 patients were allocated to the Favipiravir group (116 assessed) while 120 to the control group (120 assessed). Seven day's clinical recovery rate was found to be 55.86% in the control group while 71.43% in the Favipiravir group (P = 0.0199). The latency to fever reduction and cough relief in the Favipiravir group was found to be significantly shorter than that in the control group (both P<0.0001). Furthermore, no statistical difference was noted of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P>0.05).[19]

• **Japanese observational study —** A multicenter observational study was conducted to examine and understand the clinical course of moderate and severe COVID-19 patients receiving Favipiravir. In this study, a total of 2,158 patients received Favipiravir. Largely, in mild to moderate COVID-19 patients, clinical improvement with Favipiravir was observed in up to 74% by day 7 of treatment which further improved to 88% by Day 14 of the treatment.[20]

• **Russian Study basis approved by the Russian Ministry of Health** — A total of 390 patients (Part 1-60 and Final part 360) were considered in a study conducted in Russia. The median elimination time for the SARS CoV-2 observed was 4 days with Favipiravir while 9 days with the standard therapy. In the favipiravir group, on day 4 of treatment, 65% of patients became RT-PCR negative, on day 10 of treatment, 90% of patients were found to be real-time PCR negative for SARS CoV-2. Approximately 68% of patients in the favipiravir group reached fever resolution on day 3 as

opposed to those on standard therapy on day 6.The overall reported efficacy of favipiravir was observed to be >80% with regards to virus elimination proven with negative test report and symptomatic improvement.[21]

• **Indian Favipiravir Clinical Trial —** A randomized, multi-centric study was conducted in India across 11 centers to assess the efficacy and safety of Favipiravir with the standard of care vs. standard of care alone in mild to moderate COVID-19 patients. The sample size considered was 150, further consisting of 90 mild and 60 moderate patients). The study population chosen consisted of hospitalized patients with confirmed RT-PCR positivity. The dosing regimen considered was Favipiravir tablets 3,600 mg (1,800 mg BID) on Day 1 and 1,600 mg (800 mg BID) from day 2 onwards for up to a maximum of 14 days, in conjunction with supportive care.

• The results from the phase 3 study demonstrated numerical improvements in primary endpoint with 28.6% quicker viral clearance in the overall population as quantified by the median time until cessation of oral shedding of virus in the Favipiravir treatment arm compared to those in the control arm. The results also pointed out 40% quicker achievement of "clinical cure" which was in turn defined as the physician's assessment of normalization of clinical signs namely temperature, oxygen saturation, respiratory rate, and cough. Also, it was observed that there was a statistically significant reduction in median time to clinical cure in the Favipiravir treatment arm (3 days [95%CI 3.0, 4.0]), compared to the control arm (5 days [95%CI 4.0,6.0]) (HR 1.749 [95% CI 1.096, 2.792]; p=0.029). About 69.8% of patients in the Favipiravir treatment arm accomplished clinical cure by Day 4, which was statistically significant as compared to 44.9% observed in the control arm (p=0.019). In patients who showed clinical deterioration and required oxygen support, those receiving Favipiravir exhibited a longer median time to first-time use of oxygen of 5 days (95%CI 1.0,6.0) versus 2 days (95% CI 1.0-4.0) in the control group. Favipiravir was found to be well tolerated with no serious AE. AEs were reported in 26 patients in the favipiravir treatment group (35.6%) vs 6 patients in the control group (8%). Most of these AEs were mild to moderate and none resulted in drug discontinuation or dosing adjustments. The most commonly encountered AE was asymptomatic transient increases in uric acid (12 patients in the Favipiravir treatment arm while none in the control arm); most resolved in the first follow up. There was minimal GI disturbance and no clinically significant differences were found between the treatment groups.[22]

Limitations :

Based on the currently available evidences, favipiravir has shown clinical benefits and acceptable tolerability profile in mild to moderate cases of COVID-19. Nonetheless, members of expert panel of 'Academy of Advanced Medical Education' opine that more well-designed, multicentric, double-blind controlled trials with a higher number of sample size are urgently required to understand the extent of benefit with favipiravir in the management of COVID-19 patients. It is not yet clear whether favipiravir has any role in severe cases of COVID-19 and whether it reduces need of ventilatory support and affects mortality. Also, the dose and duration of favipiravir treatment are higher and longer, respectively, in COVID-19 patients than in influenza, therefore, close monitoring of any adverse events should be done in patients using favipiravir as part of phase 4 study or post marketing surveillance exercise.

Disclosure and Acknowledgement :

Academy of Advanced Medical Education is thankful to Lupin Ltd., Mumbai for providing logistic & technical support to conduct the consensus meeting. No other financial grant was received by any of the panel members for developing this consensus statement. Academy is also thankful to Dr Vinay Purohit from Lupin Ltd. for his assistance in providing recent scientific literature and data to develop this paper.

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Drug Corner

Effect of Zolpidem Tartrate on Sleep Quality and Health-Related Quality of Life in Indian Patients with Insomnia and Hypertension

Rajiv D Karnik[1], Neha Haris[2]

Objectives : Insomnia and hypertension often coexist. The objective of this study was to assessthe effectiveness and safety of zolpidem tartrate onsleep quality and overall quality of life (QoL) in Indian patients with insomnia and hypertension.

Material and Methods: Patients experiencing sleep disturbances for at least 3 nights/week, having insomnia severity index (ISI) score of ≥8 at screening, and a clinical diagnosis of hypertension were enrolled. The main outcome measuresweremean change in the severity of insomnia symptoms (ISI) and RAND 36-Item Health Survey scores (RAND-SF36) on Day-21compared to baseline. Adverse events (AEs) were recorded for safety assessment.

Results: A total of 41 (91.2%)out of 45enrolled patients completed the study. 21-days of treatment with zolpidem tartrate significantly reduced the ISI score by -10.07 (p<0.0001) compared to the baseline mean (SD) score of 14.73 (4.33). Significant improvement in RAND-SF36mean scores were also evident. Role limitation due to physical and emotional health score increased significantly(p<0.0001) by 51.22 and 55.28, respectively, energy score by 20.49 (p<0.0001), emotional well-being score by 7.41 (p<0.01), social function score by 22.26 (p<0.0001), pain score by 22.62 (p<0.0001), and general health score by 4.88 (p<0.01); physical function scoreincreased marginally by 3.29(p>0.05)over the 21-daysstudy period. The commonly reported AEs were fatigue (4.44%), somnolence (4.44%), and headache (2.2%), which were mild and resolved subsequently.

Conclusion :The study demonstrated that zolpidem tartrate improved sleep quality, health-related QoL, and was found to be well-tolerated in Indian insomniac patients with hypertension (CTRI/2018/12/016688).

[*J Indian Med Assoc* 2020; **118(9):** 77-84]

Key words **: Zolpidem, insomnia,hypertension, sleep, quality of life.**

Characterized as a disturbance in sleep initiation or maintenance, insomnia is one of the most commonly encountered sleep disorder in medical practice.[1] Insomnia is often undiagnosed and neglected due to lack of consultation in primary care settings.[2] Disorderaffects 30% to50% of the general adult population[3].In India, the prevalence of insomnia varies between 14 to 18.7% in general population.[4] Etiology of insomnia is not clearly understood, and involves many factors including environmental, genetic, psychological, and behavioral, leading to a state of hyperarousal.[5] Insomniais a risk factor for impaired daytime function, the development of other medical and mental disorders, and increased health care costs.[5]

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Received on : 04/09/2020
Accepted on : 10/09/2020

Editor's Comment :

- **Zolpidem at the recommended dose is effective in improving sleep quality and consequently QOL and day-to-day functioning in insomniac patients with hypertension. Drug is well-toleratedand may help in BP control in new-onset hypertension.**

Although long-term sleep loss is often secondary to somatic or psychiatric illness[6], it appears that insomnia may also play a central role in the pathogenesis of somatic illness and metabolic dysregulation[7].Insomnia has been particularly associated with cardiovascular diseases and its precursors such as hypertension and non-dipping blood pressure (BP).[8] Blood pressure physiologically decreases during sleep, a process known as dipping.[9,10] Studies have shown that day-to-night and nighttime regulation of BP appears to be closely linked with autonomic changes happening during the wake-sleep cycle.[11,12] This suggests that BP is especially sensitive to sleep disturbances.[10] Hypersecretion of adrenocorticotropic hormone, cortisol and

catecholamine has been reported in patients with insomnia symptoms, suggesting the over activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system (SNS); which provides a biological basis for the co morbidity of insomnia and hypertension.[13]

The recent evidence suggests that the increasing prevalence of hypertension might be related both to an increased prevalence of insomnia and to the poor sleep quality/ duration.[14-16] Additionally, anxiety that often accompanies sleep disorders is associated with increased BP, a known risk factor for cardiovascular events.[16,17] This indicates that the pharmacotherapy for sleep disorders and insomnia may have beneficial effects on BP.[16,18,19] Furthermore, several experimental studies have suggested that certain sleeping pills may decrease BP or SNS activity.[16] However, only a few researchers have studied the association between hypertension and insomnia treatment, and the impact of this treatment on BP.[18,19]

The drugs primarily used for insomnia treatment include benzodiazepines, non-benzodiazepines hypnotics, ramelteon, and antidepressants such as doxepin.[2] Benzodiazepines formed the mainline therapy for insomnia for many years. However, associated side-effects and addiction potential has restricted the use of benzodiazepines.[20]Among non-benzodiazepines, zolpidemtartrate is the highly prescribed drug for the short term treatment of insomnia globally.[2,21]Huang *et al*., demonstrated that zolpidemtartrate, through improvements in sleep quality, stress status, and activation of the SNS, could significantly help the conversion of non dippers to dippers.[18] However, there is no data regarding the use of zolpidemtartrate in Indian patients suffering from co-morbid insomnia and hypertension. The present studywas designed with the objective to obtain insights on the effectiveness and safety of zolpidemtartrate in Indian patients with insomnia and hypertension over a period of 21-days.

Study Design and Population :

This was a prospective, single-center, open-label, non-comparative study (CTRI/2018/12/016688) conducted between May 2019 and September 2019at Dr. Karnik's Cardiac Clinic, Mumbai, India. Outpatients of both sexes, between 18-65 years of age, experiencing sleep disturbances (difficulty in sleep initiation or middle of the night awakening or early morning awakening or poor quality of sleep) for at least 3 nights/week, insomnia severity index (ISI) score of $\geq$8 at screening, with a clinical diagnosis of hypertension, and willing to sign informed consent for study participation were enrolled in this study.

Patients on prescription and non-prescription sedative drugs for more than 2 days for sleep disturbances or to relieve jet lag and/or patients with regular change in sleep schedule by at least six hours within the last 28 days preceding to enrolment, evidence of any medical condition as revealed by history, physical examination or laboratory assessment which may interfere with administration or assessment of study medication, current alcohol or drug abuse, patients having history of obstructive sleep apnea, restless leg syndrome, myasthenia gravis, hepatic insufficiency, respiratory depression, other sleep disorders, patients having presence of any untreated or uncompensated clinically significant renal, endocrine, gastrointestinal, hepatic, respiratory, cardiovascular, neurologic, hematologic, oncologic, immunologic, cerebrovascular disease or malignancy, cognitive impairment, symptoms of chronic/ incapacitating pain, patients having history of severe cardiac, hepatic, neurological and renal diseases within 6 months prior of screening, bipolar disorder, psychosis, major depression, unstable anxiety disorders/panic attacks, patients viewed by the investigator as not being able to complete the study, and/or patients on other CNS depressants drugs like antipsychotics (neuroleptics), hypnotics, anxiolytics/ sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anesthetics and sedative antihistamines or CYP 3A4 or CYP 1A2 inducers or inhibitors were excluded from the study. Pregnant or breastfeeding women, elderly patients having symptoms of urinary obstructions, patients having participated in a clinical trial in the last one month, and/or with any other serious disease or condition at the screening that might affect the normal sleep pattern were also not included in the study.

The total duration of the study was 21 days. Patients enrolled were prescribed with zolpidem tartrate10mg. (Zolfresh®, Abbott India Limited)at the baseline, for a period of 21 days. Progress made by the patient was reviewed on Day 21.

The study was conducted as per the good clinical practices (GCP) and the applicable national regulations to assure that the rights, safety, and wellbeing of all the participants were protected, consistent with the ethical principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from all study participants before being examined for eligibility criteria. The study protocol and the informed consent form were reviewed and approved by the relevant institutional review board before initiation of the study.

Scales used in the Study :

ISI: Increasingly being used as a yardstick of treatment response in clinical research, ISI is a brief instrument designed to measure the severity of nighttime and daytime components of insomnia.[22] Designed as a brief screening tool for insomnia, the seven-item self-report instrument rates the nature and symptoms of patients' sleep problems, and is intended both for screening purpose and for assessing the efficacy of treatment.[23]

RAND 36-Item health survey (RAND-SF36) : A set of comprehensible, easy to administer, patient-reported quality-of-life (QoL) assessment tool, RAND-SF36 is commonly used for routine monitoring and assessment of treatment outcomes in adult patients.[24]

Study Endpoints :

The primary effectiveness endpoint of the study was the mean change in the severity of insomnia symptoms, as measured by the ISI, from baseline to Day 21 post-zolpidem tartratetreatment. The secondary effectiveness endpoints included mean change in Health-Related QoL(HRQoL), as measured by RAND-SF36scores, from baseline to Day 21, post-zolpidem tartrate treatment. The safety of zolpidem tartrate was assessed throughout the treatment period of 21-days.

Statistical Analysis :

Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using paired t-test at a 5% level of significance and the corresponding p-value is presented. Data were analyzed using RStudio version 4.0.0.

Results :

A total of 45 (Male: Female—22:23) patients with mean (SD) age of 47.18 (13.25) years were enrolled in the study, out of which 41 (91.2%) patients completed the study. The demographic and baseline characteristics of patients are summarized in Table 1.Data of patients completing the study (n=41) was considered for effectiveness analysis and full data set (N=45) for safety analysis.

Mean change in effectiveness parameters in 41 patients at Day 21 post zolpidem tartratetreatmentare presented in Table 2.Compared to the baseline, there was a statistically significant reduction in the mean ISI scores (-10.07 [95%CI: -11.80 to -8.34, p<0.0001]) at 21-days. The improvement in HRQoL in the study cohort was evaluated by RAND-SF36.Compared to the baseline there was no statistically significant improvement in the mean physical function score from baseline to Day 21 visit (3.29 [95%CI: -0.89 to 7.48, p>0.05]). However, there was a statistically significant improvement in score of role limitation due to physical health (51.22 [95%CI: 36.57 to 65.87, p<0.0001]), and emotional health (55.28 [95%CI: 40.86 to 69.71, p<0.0001]), on Day 21compared to the baseline.

Table 1 — *Patient characteristics at baseline (N=45)*

Parameter	Overall (N=45)
Sex, n (%)	
Male	22(48.89%)
Females	23(51.11%)
Age (Years), mean±SD	47.18±13.25
Height (Cms), mean±SD	163.49±7.07
Weight (Kgs), mean±SD	74.50±15.74
BMI (kg/mt²), mean±SD	27.82±5.55
Insomnia Severity Index Score, mean±SD	14.91±4.18
RAND 36-Item Health Survey score, (mean±SD)	
Physical Functioning	80.33±20.49
Role Limitations-Physical health	32.22±38.30
Role Limitations-Emotional Problem	30.37±37.49
Energy/fatigue	66.52±22.36
Emotional Well Being	65.24±15.23
Social Functioning	53.06±14.88
Quality of life due to Pain	62.11±19.27
General Health	59.67±19.44
Vitals, (mean ± SD)	
Pulse (beats/min)	79.49±15.02
Respiratory Rate (breaths per minute)	20.20±0.69
Systolic BP (mmHg)	149.53±7.77
Diastolic BP (mmHg)	81.71±9.65
Patients completing study	
Patients completed the study as per protocol	41 (91.2%)
Reason for withdrawal	
Adverse Events	04 (8.8%)

The mean energy score also increased significantly (20.49 [95%CI: 12.67 to 28.31, p<0.0001]) from baseline to Day 21 visit. Likewise, compared to the baseline there was a statistically significant improvement in mean emotional well-being score (7.41 [95%CI: 3.17 to 11.66, p<0.01]) at 21-days.Compared to the baseline there was a statistically significant improvement in the social function score from baseline to Day 21 visit (22.26 (95%CI: 14.54 to 29.97, p<0.0001]). The mean pain score also improved significantly (22.62 [95%CI: 15.10 to 30.14, p<0.0001])at 21-days.Correspondingly, compared to the baseline, general health score also improved significantly (4.88 [95%CI: 1.43 to 8.33, p<0.01]), at 21-days.

Change in Pulse rate and BP of patients with <1-year and >1-yearhistory of hypertension were analyzed and are presented in Table 3.Compared to the baseline, there was no statistically significant reduction in the pulse rate from baseline to Day 21 visit in patients with <1-year of hypertension (-6.39bpm [95%CI: -13.01

to 0.23,p=0.0578]). But in patients with >1-year history of hypertension, pulse rate reduced significantly from baseline to 21-days (-7.33bpm [95%CI: -12.86 to -1.81, p<0.05]).However, compared to the baseline systolic BP reduced significantly at Day 21 in patients with <1-year (-9.26 mmHg [95%CI: -13.54 to -4.98, p<0.001]) and >1-year (-8.56 mmHg [95%CI: -12.44 to -4.67, p<0.001]) history of hypertension. But no statistically significant changes in the diastolic BP were seen from baseline to 21-daysin patients with<1-year (-0.65mmHg [95%CI: -3.69 to 4.99,p=0.7583]) and >1-year (-2.66mm Hg [95%CI: -6.30 to 0.97, p=0.1400]) history of hypertension.

Table 2 — *Mean Change In Effectiveness Endpoints after 21 Days of Treatment Compared to Baseline*

Variables (n=41)	Baseline Mean±SD	Day 21 Mean±SD	Difference (95% CI)	P value[a]
Insomnia Severity Index (ISI)	14.73±4.33	4.66±3.97	-10.07(-11.80, -8.34)	<.0001
RAND-SF36 Parameters				
Physical Functioning	79.27±21.84	82.56±27.11	3.29 (-0.89, 7.48)	0.1196
Role Limitations-Physical health	31.71±38.33	82.93±31.84	51.22 (36.57, 65.87)	<.0001
Role Limitations-Emotional Problem	30.08±37.86	85.37±28.91	55.28 (40.86, 69.71)	<.0001
Energy/fatigue	67.48±16.74	87.97±24.19	20.49 (12.67, 28.31)	<.0001
Emotional Well Being	66.35±14.15	73.76±16.49	7.41(3.17, 11.66)	<.01
Social Functioning	53.65±15.42	75.91±22.25	22.26 (14.54, 29.97)	<.0001
Quality of life due to Pain	62.75±19.19	85.37±18.16	22.62 (15.10, 30.14)	<.0001
General Health	59.27±20.30	64.15±19.13	4.88 (1.43, 8.33)	<.01

CI=confidence interval, SD=standard deviation[a]Analyzed using Paired Sample T-Test

Table 3 — *Change In Pulse Rate And Blood Pressure*

Variables	Baseline Mean±SD	Day 21 Mean±SD	Difference (95% CI)	P value[a]
Patients With >1-Year History of Hypertension (n=18)				
Pulse (beats/min)	78.33±15.39	71.00±10.09	-7.33 (-12.86, -1.81)	<0.05
Systolic BP (mmHg)	151.44±7.66	142.89±9.55	-8.56 (-12.44, -4.67)	<0.001
Diastolic BP (mmHg)	82.83±8.28	80.17±7.33	-2.67(-6.30, 0.97)	0.1400
Patients With <1-Year History of Hypertension (n=23)				
Pulse (beats/min)	79.61±15.25	73.22±8.13	-6.39 (-13.01, 0.23)	0.0578
Systolic BP (mmHg)	147.48±6.77	138.22±10.16	-9.26 (-13.54, -4.98)	<0.001
Diastolic BP (mmHg)	79.39±10.30	80.04±6.44	-0.65 (-3.69, 4.99)	0.7583

CI=confidence interval, SD=standard deviation[a]Analyzed using Paired Sample T-Test

Safety :

About 4(8.89%)patients reported 5(11.11%) incidences of AEs (N=45). The most commonly reported AEs were fatigue (2[4.44%]) and somnolence (2[4.44%]), followed by headache (01 [2.2%]).All the AEs (5 [11.11%])were mild, with unlikely relation with study medication, and were resolved subsequently. No severe or serious AEs were reported.

Discussion :

Sleep plays a key role in the regulation and functioning of the central nervous system and other physiological functions such as regulation of body temperature, metabolism, catabolism, learning, and memory consolidation.[2] Although, one fourth to one-third of the general population reports of the problem in falling or staying asleep, approximately 10% present with chronic complaints and seek medical help for the problem.[25] Untreated insomnia results in clinically significant impairment in social, occupational, or other important areas of subsequent daytime functionality.[26]

The hypothesis that insomnia symptoms increases the risk for hypertension incident over time has been well-established in several studies.[2] But, until a few years ago, the connection between insomnia with hypertension was considered to be inconsistent and discreet.[25] However, in recent years, studies using objective measures of sleep have demonstrated a significant association between the two disorders.[4,25,27-29]

Taylor *et al.* reported a 43.1% prevalence of hypertension in patients with insomnia as compared to 18.7% in individuals without insomnia.[27] Zhanet al. reported the prevalence of hypertension in patients with occasional and frequent insomnia as 43.0% and 48.0%, respectively.[28] Uchimura et al. investigated 5747 workers regarding insomnia and hypertension and reported that insomniac workers reporteda significantly higher incidence of hypertension compared to non-insomniac workers, suggesting a close relationship between insomnia and hypertension.[29]A recent study in India reported 47.2% prevalence of insomnia in adults (≥18 years) with newly diagnosed or known history of hypertension.[4]

It is proposed that the therapy aiding in satisfactory/adequate sleep is directly and/or indirectly effective in treating hypertension.[29]The two most widely used treatment strategies for insomnia are pharmacotherapy

(hypnotic medications) and cognitive behavioral therapy, though pharmacotherapy remains the primary treatment for insomnia.[30] Zolpidemtartrate was the first non-benzodiazepines drug developed to address safety concerns associated with benzodiazepines use.[31]The most widely prescribed drug for the treatment of insomnia worldwide,[2] zolpidemtartrateis characterized by a rapid onset of action as well as minimal residual and rebound effects.[32] The approved doses of zolpidem tartrate (10mg for adults, 5mg for the elderly) are found to be effective in reducing sleep latency and consequently increasing duration of sleep in insomniac patients.[33] The present study evaluated the effectiveness and safety of zolpidem tartrate in patients of insomnia with hypertension, over a medium-term observation period of 21-days.

The assessment of insomnia is multidimensional, though a clinical evaluation remains the gold standard for making a valid insomnia diagnosis; a brief and valid questionnaire can facilitate the initial screening and formal evaluation of insomnia.[34] The ISI is a brief instrument that was designed to assess the severity of both nighttime and daytime components of insomnia and is a reliable and valid instrument with good psychometric properties to detect cases of insomnia.[34] Achange in the score by $\geq$9 corresponds to a marked improvement in the ISI score rating.[34] In our study, compared to baseline, the mean ISI score was reduced by -10.07 ($p<0.0001$), suggesting that that zolpidem tartrate improved sleep quality in insomniac patients with hypertension.

The results reported in our study are consistent with published literature. In a randomized, double-blind, placebo-controlled, parallel-group multicenter trial, zolpidem10mg had a significant effect on latency to persistent sleep and sleep efficiency. The effectiveness of the drug was maintained all through the 35 nights of administration.[35] Another study assessing clinical effectiveness and safety of 4-weeks of treatment with zolpidem 10mgin perimenopausal and postmenopausal women, reported a considerable increase in total sleep time, along with a significant reduction in wake time after sleep onset and number of awakenings.[36] In a double-blind, placebo-controlled study, 12-weeks of non-nightly administration of zolpidem significantly improved sleep continuity in patients with primary insomnia. Moreover, these clinical gains were sustained over time, with no evidence of insomnia reversion.[37]

In a double-blind, placebo-controlled randomized polysomnography trial, eight months of nightly zolpidem treatment in primary chronic insomniacs significantly increased total sleep time and sleep efficiency, decreased latency to persistent sleep and wake after sleep onset, when assessed at month-1 and 8, relative to baseline and placebo.[38] A recent randomized controlled study in patients of total hip arthroplasty reported that the zolpidem 10 mg improved sleep quality effectively, and reduced perioperative anxiety and depression. Moreover, patients taking zolpidem achieved greater satisfaction and improvement in the QoL.[39]

The RAND-SF36 questionnaire can assess eight aspects of health ranging from physical to emotional well-being, social functioning, common perceptions of vitality, and role limitations because of physical or emotional problems.[24] The questionnaire has the advantage of describing the impact of the disease from a patient's point of view, instead of biological or disease-centered outcomes perceived by clinicians.[24] Sleep disorders have a considerable negative effect on the QOL of hypertensive patients, especially in the physical domain of the QOL questionnaire.[40] The result from our study also confirms this, as the mean physical function score in our study increased marginally ($p>0.05$) at 21-days.

It's known that individuals with insomnia have more health concerns that limit their physical activity, cause more body pain, and emotional difficulties, compared togood sleepers.[41] The results from our study show that 21-days zolpidemtartratetreatment improved physical and emotional health, resulting in significant improvement ($p<0.0001$) in role limitations due to physical health and emotional problem, and QoL due to painscores, at the Day-21. Mental status and emotional state are worse in insomniac patients compared to the good sleepers.[41]Twenty-one days of treatment with zolpidemtartrate in our study resulted in significant improvement in emotional wellbeing scores ($p<0.01$), resulting in an overall improvement in social functioning ($p<0.0001$), energy/fatigue ($p<0.0001$), and general health($p<0.01$) domains. In our study, improvement in sleep quality post-21-days of treatment with zolpidemtartrate contributed to the improved QOL and day-to-day functioning in insomniac patients with hypertension.

Stages 3 and 4 (N3, the third stage) of non-rapid eye movement (NREM) sleep are often referred to as deep sleep or slow-wave sleep (SWS) and are considered "restorative" period of sleep.[2] In healthy adults, approximately 20% of sleep time is spent in SWS, which is characterized by the increased vagal tone and reduced sympathetic activity which decreases heart rate, BP, and cardiac workload.[2] On an average,

BP declines by 10 mmHg or more during sleep and those not experiencing this are "non-dippers".[2] Sleep deprivation excites SNS during the night, resulting in increased BP persisting during the daytime.[2]

In a cross-sectional analysis of sleeping pill use among hypertensive (n = 5099) and normotensive (n = 6126) subjects by Sasaki *et al.*, authors observed a negative dose-response relationship between the frequency of sleeping intake and systolic or diastolic BP, in subjects not taking any antihypertensive medication.[16]This suggests that the improvement in sleep quality and duration with sleeping pill use results in decreased BP, since both poor sleep quality and shorter sleep duration are involved in the activation of SNS and the elevation of BP;[16] and also, that the use of a sleeping pill may reduce BP, independent of its effects on sleep.[16]

In our study, compared to the baseline, pulse rate reduces significantly by -7.33 bpm(p<.0001)in patients with >1-year history of hypertension and non-significantly by-6.39bpm (p>0.05) in patients with <1-year history of hypertension, post 21-days of treatment with zolpidemtartrate. However, 21-days of treatment with zolpidemtartrate, resulted in a significant reduction (p<.0001)in the systolic BP by -8.56 mmHg and -9.26mmHg, in patients with >1-year and <1-yearhistory of hypertension, respectively. The diastolic BP reduced marginally by -2.67mmHg and -0.65mmHg, respectively, in both the groups. This indicates that the improvement in sleep quality post zolpidemtartrate treatment may have a potential role in BP control in insomniac hypertensive patients.

Another randomized, placebo-controlled study has also shown that zolpidemtartratecan reduce SNS activity and nocturnal BP in hypertensive patients.[18]In a study by Huang *et al.*, poor sleepers treated with zolpidem tartrate for 30 days showed significant improvements in sleep quality and stress levels (p<0.01). Epinephrine and norepinephrine levels were also significantly reduced in poor sleepers treated with zolpidem (p<0.05).[18] Another randomized, parallel-group study evaluated the effect of zolpidem tartrate on BP and BP patterns in patients with non-scoop type of hypertension complicated with insomnia.[42]The authors reported that the 4-weeks of treatment with zolpidem tartrate 10mg in combination with levamlodipine besylate 2.5mg significantly lowered night and day time BP when compared with levamlodipine besylate 2.5mg alone (p<0.05). Combination treatment also effectively retrieved the non-scoop type of BP in study cohort.[42]

The general safety of zolpidemtartrate has been studied in data obtained from both adult and elderly population during its clinical development phase and post-marketing experience.[43]The drug has been reported to be well-tolerated when administered as per prescribing information.[38]Also, there is little evidence of tolerance to the hypnotic effects of zolpidemtartrate, or rebound insomnia or withdrawal symptoms after discontinuation of the drug when prescribed atthe recommended dose.[43]In the present study also zolpidem tartrate treatment was well-tolerated. The AEs observed in our study were fewer than compared with AEs reported with the use of zolpidem tartratein other studies.[44-47] No severe or serious AEs were reported. The most commonly reported AEs in our study were fatigue, somnolence, and headache.

In conclusion, the result of this single-center, open-label, prospective study suggests that 21-days treatment with zolpidem tartrate resulted in significant and clinically relevant improvements in insomnia symptoms and QoL, as determined by ISI and RAND-SF36 scale scores, respectively. The results also emphasize the plausibility that improvement in sleep quality may aid in BP control in new-onset hypertension. The drug was effective and well-tolerated in patients with insomnia. However, while interpreting the result of this study some limitations such as small sample size, not statistically powered, and absence of control and/or comparator need to be considered. Further studies on a larger sample size, assessing the 24-hr ambulatory BP monitoring is warranted to substantiate our findings.

Acknowledgment :

The authors thank the patients and study teams involved in the study. The authors also thank medONE Pharma Solutions, Gurugram, Delhi NCR, India, for medical writing support for the development of the manuscript.

Conflict of interest :

This Investigator-Initiated Study was funded by Abbott India Ltd. The views expressed and stated in this publication are the views of the authors and not of Abbott India Ltd.

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Mediquiz

Series - 8

The name of Cities in Medicine

Rudrajit Paul
Quiz Master

1. Which of the following clinical conditions is diagnosed by the PARIS criteria?

a. Autoimmune hepatitis-PBC overlap syndrome
b. IgG4 associated disease
c. Autoimmune pancreatitis
d. Renal tubular acidosis

2. Which of the following is diagnosed with the help of ROME criteria?

a. Inflammatory bowel disease
b. Irritable bowel syndrome
c. Premalignant lesions in the colon
d. Hypoparathyroidism

3. Which disease is associated with the ***WEST HAVEN*** *criteria?*

a. Sjogren syndrome
b. Myocarditis
c. Pleural mesothelioma
d. Hepatic encephalopathy

4. Which clinical condition is associated with NEW YORK criteria ?

a. Rheumatoid arthritis
b. Renal vasculitis
c. Psoriasis
d. Ankylosing spondylitis

5. Which disease is associated with the BERLIN criteria?

a. Hypopituitarism
b. Scrub typhus
c. ARDS
d. Polychondritis

6. Recently, the "OSLO DEFINITION" has been formulated for which condition?

a. SLE nephropathy
b. Kaposi Sarcoma
c. Celiac Disease
d. TSH secreting tumour

7. Which public health topic was addressed in the DOHA declaration?

a. Right to essential medicines
b. Ethics in organ transplant
c. Right to safe drinking water
d. Palliative care in oncology

8. Which disease is diagnosed with the help of MANCHESTER criteria?

a. Polyposis of colon
b. Neurofibromatosis
c. Autoimmune encephalitis
d. Myocardial sarcoidosis

(Answer : next page)

Answer : Mediquiz

Answers : -

1. A

The Paris criteria is used for diagnosis of AIH-PBC overlap syndromes. These syndromes are rare and may be resistant to immune-suppressive therapy. The sensitivity and specificity of this criteria are both >90%.

2. B

The irritable bowel syndrome is diagnosed with the help of Rome criteria. The criteria were first published after a conference in Rome in 1988. But it has been modified over the years and new versions published. Currently, we are using the Rome IV criteria.

3. D

The West Haven criteria is used for diagnosis/ classification of hepatic encephalopathy. The classification system (also called modified Parsons-Smith classification) is given below:

Grade 0	No abnormality detected (mHE)
Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
Grade 2	Lethargy
	Disorientation for time
	Obvious personality change
	Inappropriate behavior
Grade 3	Somnolence to semistupor
	Responsive to stimuli
	Confused
	Gross disorientation, bizarre behavior
Grade 4	Coma, unable to test mental state

(Source: Dove Medical Press)

4. D

Ankylosing spondylitis is diagnosed with the help of modified New York criteria. It has both clinical and radiological parameters

5. C

The Berlin criteria has been devised for ARDS in 2012. This criteria also includes classification of ARDS based on P/F ratio.

6. C

The Oslo definition has been formulated by a group of researchers for Celiac Disease. They have done extensive electronic database search for this purpose.

7. A

The Doha declaration is a landmark victory for public health activists of the world. By this agreement, a country is now able to grant licenses for drug production, in contravention of international intellectual property act, for public health emergencies.

8. B

The Manchester criteria was devised to diagnose NF type 2.

There are only two sorts of doctors: those who practice with their brains, and those who practice with their tongues.

— William Osler: 1914 Quote

Letters to the Editor

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

Special Corresponding

"Hypertensiologists" — The Need and Necessity in India

Sir, — Hypertension and diabetes mellitusare increasingly emerging as public health problems in developing countries like India.[1]According to evidence, the crude prevalence of diabetes mellitus (DM) and hypertension (HTN) has been reported to be 7.5% and 25.3%, respectively.[2]The prevalence levels for both these conditions in India are high across all geographical locations and socioeconomic groups in middle as well as old age groups.[2]According to the Global Burden of Diseases Study 2016, diabetes and HTN accounted for 3.1% and 16.7% of total deaths in India, respectively.[3,4] Moreover, diabetes accounted for 10 million disability-adjusted life years (DALYs) while HTN accounted for 39.4 million DALYs in the same year.[3,4] Also, HTN accounts for 57% of all stroke mortality and 24% of all coronary artery disease mortality in the country and isthe most important risk factor for cardiovascular morbidity.[5,6] An important point to be noted is that these conditions often share a significant overlap in underlying risk factors.[7] Approximately 75% of adults with DM also present with HTN, which could subsequently exacerbate the associated morbidity and mortality.[7,8] HTN and DM are both complex and heterogeneous phenotypes related with a high risk of life-endangering cardiovascular disease.[9]

In the past few years, various developments have occurred and are still emerging in the field of management of DM. Unfortunately, the same has not been observed for HTN in India. Taking into consideration the high magnitude of undiagnosed or untreated HTN cases in the country, there is a substantial lack of methodical screening and awareness programs to detect undiagnosed cases, provide early interventions and implement regular follow-ups.[10] Till date, there is scarce large-scale population-based evidence from India with respect tovarious stagesranging from screening to efficacious control of HTN.[11] There is a need to improve HTN care by targeting, rural populations, and those with low economic status, since these population groups are likely to get lost at each step of the HTN control cascade.[11]

There is an absolute necessity to reinforce the healthcare system in India and to focus on significantly improving HTN screening and treatment to decrease cardiovascular risks.[12] This would imply strengthening health careat primary, secondary and tertiary levels, integrating prevention, diagnosis and appropriate treatment.[13] Notably, vigor oustraining, regular enrichment and updating skills of health professionals is imperative for delivering better HTN related-care.[13] Moreover, provision of specialized clinics for HTN with trained specialists (Hypertensionologist) is required for addressing the current needs in urban as well as rural areas across the country. Such clinics equipped and powered with "Hypertensionogists" would effectively help in reducing the morbidity and mortality related with this condition. Furthermore, there is a severe shortage of well-trained specialists in India, especially in the rural areas; this needs to be addressed on priority.[14]

Most importantly, the health care system must take efforts for enhancing health education and increasing awareness on HTN to improve resultant outcomes.[13,15] These efforts can begin with simple measures like promoting self-blood pressure monitoring (SBPM) at home. As per evidence, SBPM has led to improved patients' awareness of blood pressure (BP), bettercontrol rate of BP and superior antihypertensive drug adherence.[11] SBPM needs to be focused largely to optimize the management of HTN patients. Likewise, accurately validated devices for BP measurement must be present at all health facilities and made accessible to all healthcare professionals.[13]

Along with SBPM and pharmacological measures, non-pharmacologic interventions also need to be incorporated for favouring effective BP reduction. Non-pharmacological interventions aid in decreasing the daily dose of medications and delaying the progression from pre-hypertensive to hypertensive stage.[17] These measures include lifestyle changes such as dietary modifications, regular exercise, relieving stress, and limiting consumption of alcohol.[17] Also, population-based preventive approaches combined with evidence-based therapeutic approaches focused on early recognition and treatment may prove to be beneficial for thepatient population.[13]

Inspite of being highly prevalent and more dangerous, HTN is a neglected entity and significantly less identified, treated and succeeded. Currently, we do have potential scope to tackle the numerous challenges pertaining to HTN management. Ensuring proper training of existing physicians, setting up exclusive HTN clinics operated by "Hypertensionogists" increasing patient awareness, implementation of home BP monitoring and good lifestyle modifications etc. could definitely help in achieving good control of HTN. Just like Diabetes and Diabetologists, creating Hypertension as sub specialty of medicine and creating more Hypertensionologists will aid our sincere efforts and appropriate therapeutic approaches, to considerably reduce the growing chronic burden of HTN and its catastrophic consequences in the country.

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Tirupur, Tamilnadu **A Murugunathan**

Effect of the Crisis Arising due to COVID-19 Pandemic in Patients with Hematological Disorders

Sir, — These are unprecedented times. A novel disease has gripped the world and brought it to a standstill. The term 'lockdown' is now a familiar term in every household. As the world struggles to adapt to the new ways of life, some are being faced with more difficulties than others. Patients having chronic or terminal illnesses, such as, cancer, chronic renal disease or collagen vascular diseases- for which, they require regular follow up with a doctor, at a hospital, for life-saving medicines or procedures, are being severely affected.

We wish to share our experiences regarding the patients who attended our Outpatient department (OPD) during the Covid-19 crisis after the Government of India declared a complete lock-down on movement of people and transportation from the 25th of March onwards[1].

Our OPD noted a significant reduction in footfall. We give here an account of 440 patients who attended our Hematology OPD in the 1st 45 days of lockdown (25th March-8th May, 2020)[1,2], a drastic reduction of79-81% as compared to previous months (Fig 1A). Out of the 440 patients, 19 patients came for more than one consultation, while 421 patients attended only once.

Our centre is a super-speciality centre for Hematology and patients visit us from all over Bengal including, neighbouring states and countries. However, as depicted in Figure 1B, fewer patients attended from farther districts or states during this period. Even within Kolkata, fewer patients were noted. A total of 104 new patients (24.7%) visited our OPD, most of whom required admission or urgent interventions, such as, immediate blood transfusions or management of acute leukemia (n=37).

During this period, our in-patient, out-patient or Day care facilities, continued as usual. All the staff, including doctors, had rotational duties. However, gradually as lockdown progressed, blood products became scarcer, and outsourcing certain investigations (of parameters not tested at our institute), became difficult.

Though hospital facilities remained functional, many hematological malignancy patients who had been receiving maintenance chemotherapy on a Day care basis, or were due for in-patient admission, failed to arrive. Most stayed away from hospitals, unless it was a medical emergency or they were out of medicines. The reasons ranged from lack of transportation to general fear among patients, and their relatives, regarding this novel disease. Patients realized the need for social distancing and avoidance of crowded places, unless absolutely necessary. While many postponed their dates on their own volition, many were forced to do so in view of distance, lack of adequate transportation or accompanying persons. Of the patients who reached the hospital, many had made high monetary payments to procure appropriate transport. Few others walked. For instance, one 60-year-old gentleman walked for 7km to reach our OPD.

This delay in receiving adequate therapeutic interventions is detrimental for patients with hematological diseases. Patients with leukemia or lymphoma whose treatment is being delayed due to the current pandemic are losing their chance at achieving disease remission.3Many patients with chronic hematological neoplasms, such as Chronic myeloid leukemia, who failed to attend the hospital in order to collect

medicines, risked a break in therapy, thus, jeopardizing the disease prognosis. Many Thalassemia patients failed to attend Hematology Department for their scheduled blood transfusions and those who could attend, had difficulty arranging for blood products for transfusion. Patients with diseases such as, Aplastic anemia, who require transfusional support as part of their treatment, also faced similar difficulties in getting admitted for life-saving blood transfusions. Even patients with Hemophilia who were leading a normal life by receiving regular weekly prophylaxis, could not attend for their scheduled dosages, and others were unable to attend the hospital, in spite of suffering from a hematoma which necessitates immediate Factor replacement therapy.

Patients with hematological malignancies or bone marrow failure syndromes are immuno-compromised and naturally more susceptible to infections, including SARS-CoV2 infection[4,5]. These patients face more difficulties than normal population, and require to practice stringent infection control measures.

In conclusion, our observation highlights how Covid-19 disease is more than one disease. The various indirect effects of this disease are also affecting our patients with hematological diseases, as many patients require to attend the hospital physically in order to get therapy. Educating our patients regarding precautions to be taken during the current Covid-19 pandemic, might encourage them to seek adequate and timely medical advice, without being unduly scared.

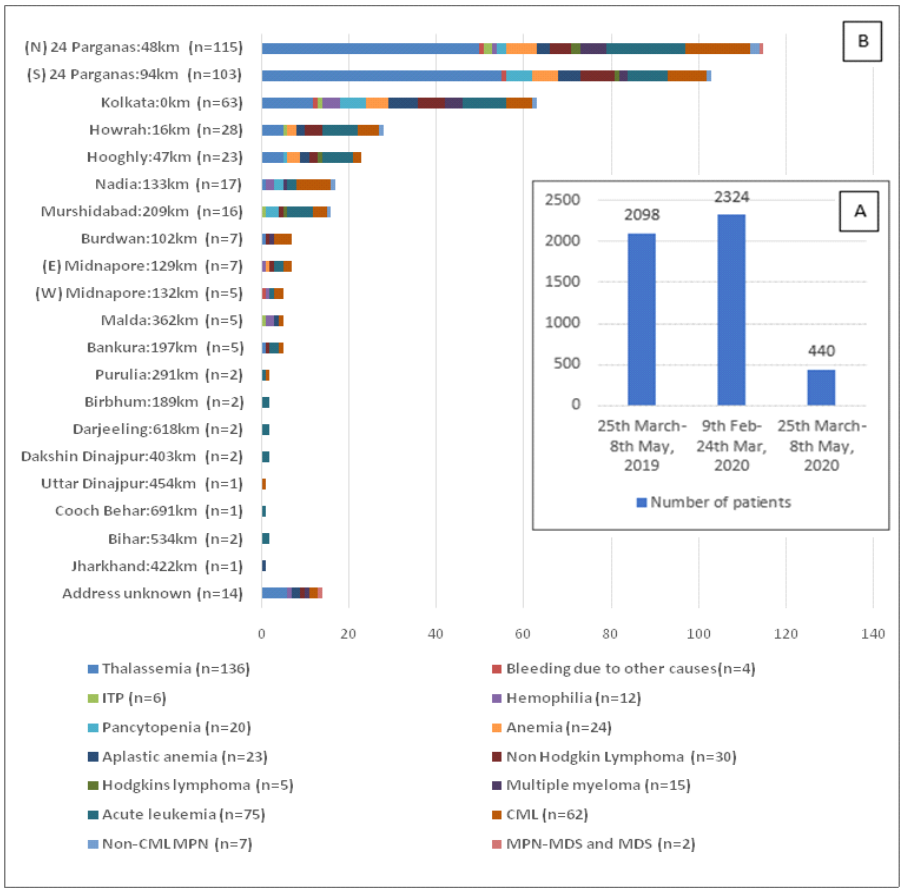

Fig 1A — Comparison of the number of patients who attended the Haematology OPD at NRS Medical College during the i) same time period in 2019, i.e. 25th March-8th May, 2019; ii) 45days immediately preceding the lockdown, 9th February-24thMarch, 2020; and, iii) 45days since the start of lockdown in India, i.e. 25th March-8th May, 2020.
Fig 1B — Demographic distribution of 421 patients along with their diseases, based on the average distance travelled to reach NRS Medical College situated in Kolkata, from the different districts of West Bengal and neighbouring states of Bihar and Jharkhand. The numbers within brackets denote the number of patients. The average distance of each district and state from Kolkata is mentioned in kilometres (km). Abbreviations: ITP=Immune thrombocytopenia, CML=Chronic Myeloid Leukaemia, MPN=Myeloproliferative Neoplasm, MDS=Myelodysplastic Syndrome

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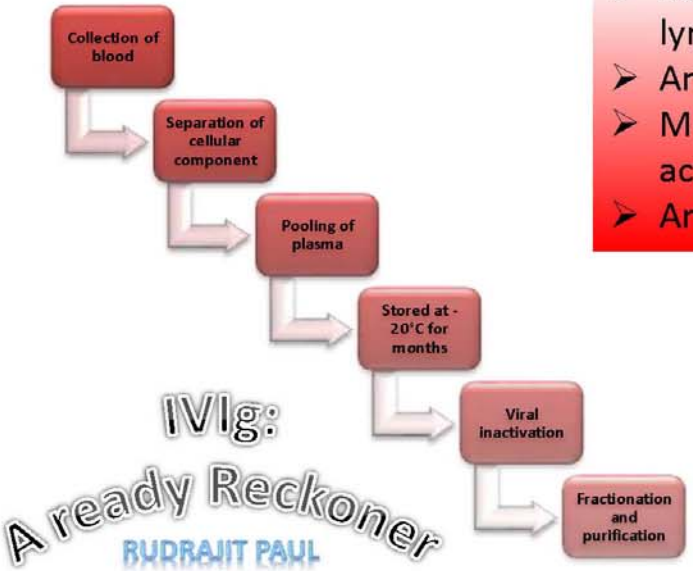
What is it?

A blood product prepared from pooled serum of multiple donors. Contains the globulin fraction of blood



How does it work?

- Antibody mediated neutralization of antigens and super-antigens
- Suppressing proliferation of T cells
- Inducing apoptosis of lymphocytes (anti CD95 action)
- Anti-Idiotypic antibody action
- Modulation of complement activity
- Anti-cytokine action

Most common dose:
2 g/Kg body weight divided over 2—5 days

IVIg: A ready Reckoner

RUDRAJIT PAUL
&
JYOTIRMOY PAL

Indications: -

FDA approved—

- Primary Immunodeficiency
- CIDP
- Kawasaki Disease
- ITP
- CLL
- Pediatric HIV etc...

Off-label--

- Grave's Disease
- GBS
- Hemolytic Anemia
- Pemphigus
- Inflammatory myopathy

Side effects: -

Hypersensitivity reaction
Aseptic meningitis
Acute renal failure
Hemolysis (RARE)
TRALI

Use in pediatric and pregnant population?

Only if benefit outweighs risks (E.g. severe GBS with impending respiratory failure)

CAUTION!!!

After IVIg use, all serological tests may be false positive for 1—2 weeks

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Registration No. KOL RMS / 476 / 2020 - 2022

RNI Regd. No. 2557/1957
Vol. 64, No, 09, September 2020, Kolkata

Date of Publication : 15th September 2020

If not delivered please return to
Journal of the IMA (JIMA)
53, Sir Nilratan Sarkar Sarani,
(Creek Row), Kolkata - 700014

Printed and Published by **Dr Sanjoy Banerjee** on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata - 700009 and Published from Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014, Editor : **Dr Jyotirmoy Pal**