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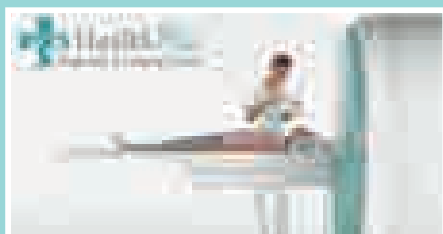
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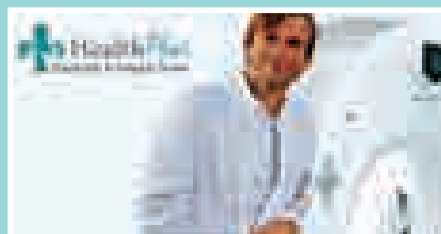
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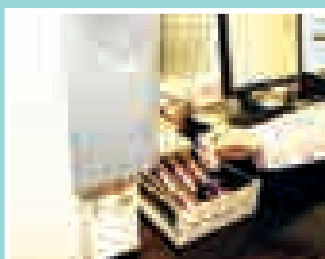
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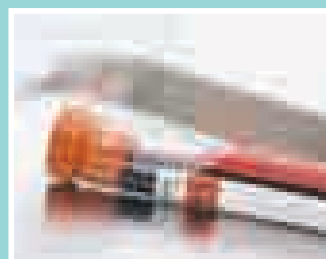
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Indian JOURNAL of CLINICAL PRACTICE

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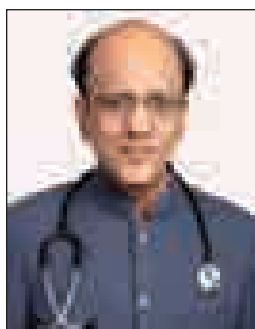
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Dr KK Aggarwal
5th September 1958 - 17th May 2021

HCFI DR KK AGGARWAL RESEARCH FUND

HCFI Round Table Expert Zoom Meeting on "Are People Adopting COVID-appropriate Behavior During Unlocking and School Reopening"

8th June, 2021 (1 am-2 pm)

KEY POINTS OF HCFI EXPERT ROUND TABLE

- Many people still do not follow COVID-appropriate behavior. In view of the emerging Delta plus variant and the rapidly spreading Delta variant, there is definitely a possibility of a third wave, which may come in few weeks.
- Schools have been closed for almost 2 years now. This has affected education as not more than 50% students are able to join online classes.
- As the second wave is receding with unlocking going on, COVID-appropriate behavior is very important.
- Despite awareness at different levels, it is observed that there is poor compliance to COVID-appropriate behavior. Initially during the first wave, precautions like wearing mask/face shield, hand washing, physical distancing, avoiding crowds were being followed, but now they are not being adhered to strictly.
- Appropriate masking, social distancing and community behavior are all very relevant as regards COVID-appropriate behavior.
- We have to improve ourselves in totality; not just citizens but also those entrusted with the responsibility of implementation of COVID-appropriate behavior such as masking in public places and become responsible citizens.
- Wearing masks not only means protecting others from the infection, but also protects oneself.
- Each of the three layers of the mask has a different function to perform. The innermost layer absorbs the secretions of the wearer, the middle layer is the filter and the outer layer is splash resistant but allows air to penetrate. The fabric mask must also have three layers. Hence, standardization of masks is important.
- Double masking must be done. Communication about proper masks, including double masking, has to percolate down to the last mile.
- A distance of 3 feet at least is desirable to be on the safe side, but this may not be practically possible always.
- Responsible and willing citizens can be empowered and recruited into the system to make up for shortage of regulatory staff.

- When implementing regulations that are being mandated as law such as masking, it is also important to see if the people have enough resources to buy masks, can they maintain physical distancing of minimum 3 feet in their circumstances, have they been trained for regular hand washing and can afford to buy soaps?
 - Affordability and accessibility must be ensured before implementing a law.
 - If provisions are not made available to the consumer, there is bound to be disobedience.
 - To increase the success rate of adherence to COVID-appropriate behavior, it is not the penalties that will help. They are only a last resort option.
 - Counseling is not given enough importance in our society. We have to bring in an environment that is more all-encompassing and helping people to get reformed.
 - IIT Mumbai alumni are making short videos of COVID-appropriate behavior in all languages to educate people and are offering them to all NGOs free of cost. While it is important to educate people, it is also important to enable them. So, information about how quality masks can be sourced should also be provided simultaneously.
 - The procurement system should be made more transparent and accountable.
 - General protocols to be followed by people for every sector should be defined and published by regulatory authorities.
 - In Kerala, gazetted officers of various departments have been appointed as sector magistrates to monitor and enforce implementation of COVID containment measures. They have the power to charge a fine as penalty for violation of containment measures.
 - Instead of self-declaring one's COVID status, people should be asked to fill in a questionnaire with questions such as their purpose of going out, high risk people in the family, etc. This will make the person aware that he and his family are at risk if he goes out.
 - Vaccination should be made a criterion in offices, etc.
 - Educational institutes should now be opened with precautions in place.
 - All higher education institutions can be opened; teachers and students who have taken both doses of the vaccine can be allowed to come. Schools can be opened in shifts.
 - Closure of schools has hampered many milestones of young children, including cognitive domain because of interaction with electronic devices at a very young age.
 - Staggered schooling should be started. Children should be brought to schools in rotation. The concept of bio-bubble can be brought in schools also. Interaction is very important for children as otherwise it will affect their mental health and development.
 - This is the time when we can contain the third peak; there have to be strict containment measures at all levels to prevent spread, there have to be strict fines.
 - There are about 48 cases of the Delta plus variant in the country (at the time of meeting). There is an apprehension that it has high transmissibility, it attaches strongly to the lung receptors and may not respond to monoclonal antibodies. Also, it may have immune escape. In Maharashtra, level 3 restrictions are in place.
 - Other people such as home guards, school teachers can be authorized, by order of the government, to fine people for not wearing a mask.
 - The Disaster Management Act and the powers within the Act regarding offences and penalties were also discussed.
 - Self discipline is the only way.
- Participants:** Dr AK Agarwal, Dr Ashok Gupta, Dr KK Kalra, Prof Bejon Misra, Dr Anita Chakravarti, Dr Jayakrishnan Alapet, Dr DR Rai, Dr Ravi Kapur, Ms Balbir Verma, Ms Ira Gupta, Mr Saurabh Aggarwal, Dr S Sharma

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Importance of WASH in COVID-19 Pandemic

DHANANJAY MANKAR*, TANMAY ILAME†

ABSTRACT

Out of quite a few zoonotic disease outbreaks in the last two decades, coronavirus disease 2019 (COVID-19) has left no stone unturned. COVID-19 pandemic demanded a reassessment of the existing norms within the national health systems. It has prioritized the importance of water, sanitation and hygiene (WASH) quality to protect human health during any infectious disease outbreak. Endorsing the best WASH and waste disposal practices on the individual, community and institutional level is crucial for preventing the spread of disease by safeguarding public health. In addition to strict social distancing norms and wearing a face mask in public places, the promotion of good hygiene, particularly handwashing with clean water and soap, is equally important. Healthcare providers are playing a critical role during the pandemic. Similarly, the increased responsibility of water utility personnel and sanitation workers, which directly enable the hygiene practices that limit the spread of the novel COVID-19 virus, is also essential.

Keywords: COVID-19, water, sanitation, hygiene, waste management, public health, environmental health

The global pandemic of coronavirus disease 2019 (COVID-19) has challenged basic hygiene behavior and related facilities. It has placed hygiene at the center of disease prevention. The intensive infectious nature of COVID-19 has led to the requirement of rigorous infection prevention and control (IPC) to reduce transmission in a healthcare facility.¹ However, billions of people living in developing countries lack safe drinking water and reliable water access even for basic handwashing.² The provision of safe water, sanitation and hygiene (WASH) with proper waste management facilities plays an essential role in the prevention of the disease. Consistent WASH and waste management practices in communities, homes, schools, marketplaces and healthcare facilities help to prevent human-to-human transmission of pathogens, including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.

The transmission of the disease majorly depends on the extent of contact with the infected individual. The main route of infection and transmission of the disease is the

same through the respiratory tract, respiratory droplets from the infected person being the potential cause of the spread of the novel COVID-19 virus. Passive transmission pathway follows the presence of respiratory droplets on surfaces where the virus could remain viable. The immediate environment of an infected person can therefore serve as a source of transmission.³ The World Health Organization (WHO) recommends the promotion of good hygiene, especially regular handwashing with clean water and soap, to prevent the transmission of the virus.⁴ Frequent and correct hand hygiene is one of the most important measures to prevent infection. The practice of handwashing at the right time, using the right technique with either alcohol-based hand sanitizer or soap and water is essential.³

WATER AND COVID-19

Access to safe drinking water is among the basic human rights and is a necessity for a healthy life.⁵ Governments of many developing countries consider the provision of safe water supplies as one of their major responsibilities. In developing countries, most people do not have access to safe drinking water.⁶ Between the years 2000 and 2015, urban coverage of basic drinking water services increased from 9% to 9%, while the rural coverage increased from 0% to 8%.⁷

Water Supply

The absence of the household drinking water facility and water storage facilities increases the frequency

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of going to water points or boreholes. This forced the community members to collect water daily from such sources, thus increasing their risk of contracting COVID-19. Developed countries, having more resources to tackle the diseases, highly relied on their water supply system, and fought the infection and transmission of the virus. However, in developing countries, the disinfection of public places led to the problem of water supply outage, which reveals that water is a key component in tackling the spread of the pandemic in several ways.² For some slum residents, the lockdown restrictions affected their access to clean water, which leaves the slum community vulnerable to exposure to other infectious diseases.⁸ It has been noted that unreliable water supplies have a relation with degraded domestic hygiene, which is tied to the increased spread of COVID-19 transmission through fomites.⁹

Gender and Disability

Women and girls are the primary collectors of water in the household or community. It is already known that this group is negatively impacted in terms of their education, livelihoods and personal safety. The COVID-19 pandemic has worsened the situation, and in some regions, social distancing and lockdown rules have led to a re-emergence of the role of caring for those infected with the virus falling largely on women. Additionally, members of the community that have a disability are often forgotten in water resources management. COVID-19 has brought to light the inequalities that exist in water accessibility.¹⁰

Water Treatment

It is found that water disinfection can reduce virus load as the virus is susceptible to detergents and oxidants, like chlorine and it is inactivated faster than nonenveloped waterborne enteric viruses.⁴ Not only COVID-19 but other infectious diseases can also be prevented, and health benefits realized by safely managing water services.

In places where centralized water treatment and safe piped water supplies are not available, several household water treatment technologies can effectively remove or destroy viruses, such as boiling, filtration, solar irradiation and appropriately dosed chlorine products including sodium hypochlorite and sodium dichloroisocyanurate (NaDCC).³ Water disinfection is critically important as the human coronavirus can reportedly survive for several days in tap water at 4°C-25°C.⁴

Water Management

The issues tied to water demand and supply to handle the COVID-19 pandemic have not gained serious attention. It is important to understand if there are enough water facilities in workplaces and other public places, as well as at homes for everyone for the anticipated future. This question is important since COVID-19 will likely continue for years and not just months, as per several health professionals, epidemiologists and other experts in fields related to infectious diseases. Besides the increase in the demand for water quantity, COVID-19 also poses challenges from the perspective of water quality.¹¹

In the parts of the world with fragile governments and economies and conflicts raging, water-sharing governance arrangements can be vital in keeping doors open for dialogue between riparian nations. Cooperation over water can enhance communication when broader diplomatic tensions arise between countries.¹⁰

SANITATION AND COVID-19

Sanitation is among the most significant components of community well-being as it safeguards human health, extends life spans, and benefits the economy. Sanitation is currently deployed to treat human excreta to protect human health and the environment.¹² Owing to the lack of proper sanitation and treatment of municipal wastewater, viral infections can be transmitted to the surrounding life and environment.⁸

Wastewater and Its Management

The detection of SARS-CoV-2 viral particles in wastewater is a potentially effective approach to identify and track the spread of the virus. Preliminary analysis indicates that monitoring wastewater influents at the community level may indicate the extent of the outbreak in certain population clusters, particularly in communities where mass testing may not be feasible.⁴

Recently, it was reported that the SARS-CoV-2 virus was excreted in the feces of COVID-19 patients, and from municipal wastewater in many countries including Australia, India, Sweden and, the USA.⁸ However, the risk of transmission of SARS-CoV-2 from the feces of an infected person and the feral-oral pathway appears to be low. One of the studies identified infectious SARS-CoV-2 in the urine of one patient and viral RNA has been detected in the gastrointestinal tissue.³ Human coronavirus has been reported to survive for several days in sewage at 4°C-25°C.⁴

Use of more water, as well as soap and disinfectants, for washing hands in order to control the spread of COVID-19 will eventually heighten the quantity of wastewater, with possibly even poorer quality, coming from homes, workplaces and other public places. Handling and disposal of wastes related to COVID-19 often require a large quantity of water, both during and after.

The quarantine and isolation centers used for testing and treating suspected and confirmed COVID-19 patients have been found to have a common sewerage system with the communities and cities. People are hence exposed to the tendency of using water from surface water sources that might have been contaminated with SARS-CoV-2.¹³ It is required to provide separate flush toilets or latrines that should be cleaned and disinfected at least twice daily by a trained cleaner wearing appropriate personal protective equipment (PPE). Places where pit latrines are used, efforts should be made to prevent contamination of the environment and groundwater with excreta.⁴

COVID-19 is thus bound to seriously impact the water sector, in terms of both water quantity and water quality.¹¹ The best way to tackle this problem is by separating the sewerage systems and wastewater treatment facilities of the healthcare centers.¹³ All the wastewater and sludge should be contained and treated either at the site or off-site in well-designed and managed wastewater and/or focal sludge treatment plants. Water utility personnel must be informed well about COVID-19 preventive measures. They may wear masks, they may follow physical distancing between workers and with the public, and practice hand hygiene frequently.³

So, appropriate treatment of municipal wastewater and additional measures are vital to limit further disease transmission.⁸ This involves creating a healthy environment, reducing open defecation and encouraging hygienic practices.¹⁴

Solid Waste and Its Management

The idea of lockdown, stay-at-home policy, and other preventive measures to check the spread of COVID-19 saw an increase in production and consumption patterns of nonmedical and household-related products, including masks, gloves, thermometers, sanitizer, cleaning products, toilet papers, foodstuffs and many other things. Sudden lockdown and fear of the virus gave rise to a surge in single-use products and panic buying.

Failure to properly manage the waste generated from healthcare facilities and households may escalate the spread of COVID-19 through secondary transmission. The waste disposal practices have often been found inappropriate, and most people disposed of a used mask, gloves and other infectious wastes with household wastes instead of separate disposal. Improper management of medical waste has the potential to expose patients, health workers and waste managers to infections. Therefore, it is essential to increase the awareness level of people regarding the preventive measures of COVID-19, as well as the significance of WASH and safe practices for infectious waste disposal practices.⁸

Even during the COVID-19 pandemic, appropriate waste management must ensure continuity and functionality of waste services as well as workers, the safety of waste service workers, adjustment of recycling services to include measures that curb the spread in the collection, disposal and treatment of medical waste. Sustainable management of medical waste is difficult, especially in current times. Waste management is an essential public service that is needed to check the spread of COVID-19.¹⁵

HYGIENE AND COVID-19

Hygiene is important for keeping people healthy across the globe.¹⁶ Hygiene plays a vital role in disease prevention. However, there is a lack of access to the water supply that supports good hand hygiene and institutional cleaning, people's understanding of hygiene behaviors, and access to soap in the low-, middle- and high-income countries.⁹ Since the transmission of COVID-19 can occur through contaminated surfaces and hands, adequate hand hygiene is essential to stop transmission.⁴

Hand Hygiene

Practicing appropriate hand hygiene can prevent respiratory illness³ and is also known to curb the transmission of viruses and bacteria causing common colds, flu and pneumonia.⁴ An increase in handwashing among susceptible communities would potentially help in preventing and controlling the spread of COVID-19.⁸

It is recommended to wash the hands thoroughly after coughing and sneezing or disposing of tissue, after coming home from public places, before cooking, before and after eating and feeding/breastfeeding, after using the toilet, or changing a child's diaper, and after touching animals.³ The simple handwashing method

is the most effective action to prevent the spread of COVID-19¹⁰

The optimal hand hygiene materials include water and soap, alcohol-based hand rub and ash. Where it is not possible to have alcohol-based hand rub or bar soap, liquid soap, or locally-made soapy water solutions can be used mixing water with detergent. The ratio of detergent to water is guided by the types and strengths of available products. Drying the hands after washing is an important part of effective hand hygiene. The moisture left on the hands after washing can be a major determinant of transmission of pathogens from hands to surfaces and the other way round. Washing and rubbing of hands and the amount of rinsing water determine the reduction of contamination on hands. A handwashing session with just 0.2 liters is sufficient.

Frequent and appropriate hand hygiene is one of the most important measures to prevent infection with SARS-CoV-2³

Home Hygiene Management Practices

In case of suspected or confirmed cases of COVID-19 at home, caregivers and other family members must be protected from the risk of contact with respiratory secretions and excreta carrying the virus. Frequently touched surfaces in the patient's care area, such as furniture, tables, etc, must be cleaned regularly. The Patient's utensils and cutlery should be washed and dried after every use and should never be shared with others. If bathrooms are shared by COVID-19 patients and other household members, they should be thoroughly cleaned and disinfected at least once a day. Regular household soap or detergent can be used for cleaning and after rinsing, a regular household disinfectant that has 0.5% sodium hypochlorite should be applied. The person carrying out the cleaning work must wear PPE, and hand hygiene supplies should be available in households caring for COVID-19 patients.

Waste generated during home quarantine, while caring for a sick person or during the recovery period, must be put in strong bags and closed completely prior to disposal and collection by municipal waste services. Individuals collecting waste should wear PPE, including heavy-duty gloves, boots, coveralls and masks when working in confined spaces, and must have facilities that allow conducting regular hand hygiene.³

Hygiene is of crucial importance in keeping people across the globe healthy. That said, the COVID-19 pandemic has provoked radical and immediate changes

in hygiene measures. It is essential to implement stricter hygiene practices now to curb COVID-19 transmission, but this increased hygiene may be tied to a microbial cost by reducing microbial acquisition and reinoculation after a loss.¹⁶

CONCLUSION

The important role that adequate WASH and waste disposal practices play in the current pandemic cannot be overemphasized.⁸

The current outbreak of COVID-19 calls for action from governments, industry and the people to limit its spread.¹⁷ The promotion of other COVID-19 control measures such as social distancing, self-isolation, and avoidance of public places has been a challenge in low-income countries.⁴ WASH practices and usage and safe disposal of safety equipment are important to fight against COVID-19.⁸ There is a need to act urgently to overcome deficiencies in WASH, especially provide reliable, continuous piped water on-premises for all households and settings. Hygiene promotion programs, based on behavioral science, are needed that are particularly adapted to high-risk populations, such as the elderly and to particular settings like healthcare facilities, transport hubs, workplaces, etc.⁹ There is an urgent need for public awareness campaigns, suburbanization of wastewater treatment facilities, use of low-cost point-of-use water treatment systems, policy interventions and community-led total sanitation (CLTS).¹³

The development of multifaceted artificial intelligence (AI) approaches such as Wash Karo should be encouraged for Infodemic Management. Wash Karo is driven by the inevitable need to increase awareness of WASH to curb the spread of COVID-19.¹⁸ For such technological innovations, we need better use of financing instruments that will help to extend and improve WASH services.⁹

Effective public health messaging is vital to obtain social support for disease containment strategies. But it must be noted that effective public health messaging, especially to convince people to limit their activities, has to be culturally and socially competent. Public health messaging regarding a disease outbreak, such as the ongoing COVID-19 outbreak, is challenging, especially in multicultural populations.¹⁹ Therefore, it becomes important to strengthen WASH facilities to prevent and fight the pandemic situation with the help of proper drinking water, hand washing, maintaining good hygiene and cleaning and self-isolating facilities. The knowledge, attitude and practice (KAP) of healthcare

workers toward COVID-19 are critical to the success of COVID-19 response efforts.²⁰ Long-term public health policy responses are required to ensure that the ongoing pandemic does not escalate health inequalities for the coming generations.²¹

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Mefenamic Acid: The Evolution of a Versatile NSAID

SURYA KANT TRIPATHI*, PRABHU N KASTURE†

ABSTRACT

Mefenamic acid is a nonsteroidal anti-inflammatory drug (NSAID) exhibiting a wide range of anti-inflammatory, antipyretic and analgesic activities. Mefenamic acid has many unique features with the potential to discern it from other NSAID agents. Mefenamic acid is one of the most widely studied drugs for its pharmacological activity and used with its established efficacy and safety over long-term use. It has been in use for a wide range of clinical purposes and is being progressively explored for its applicability in various other diseases. The inflammasome inhibitory action of mefenamic acid makes it unique amongst all the NSAIDs. In this article, the authors have reviewed the history, evolution, physiology and clinical benefits along with the safety and long-term usage of mefenamic acid in various conditions. The article also explores the potential role of mefenamic acid in the management of COVID-19.

Keywords: Mefenamic acid, fenamates, repurposed drugs, anti-inflammatory, analgesic, antipyretic, NLRP3 inflammasome blocker, COVID-19, selective COX-2 inhibitors

Mefenamic acid is an age-old and widely used nonsteroidal anti-inflammatory drug (NSAID), known for its established antipyretic, anti-inflammatory and analgesic activities that have been significantly used over five decades. Mefenamic acid has similar modes of action and general toxicity compared to other NSAIDs; however, it possesses certain unique features that may have the potential to distinguish it from the other agents. It is used for fever management, pain syndromes, inflammatory diseases like arthritis, in certain gynecological disorders like dysmenorrhea, menorrhagia,¹ and recently repurposed in coronavirus disease 2019 (COVID-19) management. In this article, the authors have discussed the history, pathophysiology, clinical uses, long-term safety and adverse effects of mefenamic acid.

METHODOLOGY

An English-language literature search was conducted using PubMed and Google Scholar to identify relevant articles published from 2010 till April 2021. Search terms included 'mefenamic acid', 'fenamates', 'NSAIDs', 'COVID-19', 'SARS-CoV-2', 'NLRP3 inflammasome inhibition' and 'COX inhibitors'. The authors of the present review included case reports, case series, review articles, systematic reviews and meta-analyses, and randomized controlled trials. Based on the selected articles, a backward citation search was also performed to identify any relevant articles. Ongoing and planned clinical trials were identified using the search term 'mefenamic acid', 'fenamates' on the ClinicalTrials.gov website.

HISTORY OF MEFENAMIC ACID

Mefenamic acid, an N-(2,3-xylyl)anthranilic acid, was initially released in 1962 for pharmaceutical purposes and was marketed in many countries and is available in many European countries and South-East Asian countries, including India. It is a derivative of N-phenylanthranilic acid and is a member of the 'fenamate' family of NSAIDs. The drug was known early to have anti-inflammatory, analgesic and antipyretic properties.²

Fenamates were initially developed in the 1950s, at a time when the management of inflammatory conditions

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was breaking out of the old salicylate mould.¹ Human pain models were established for evaluating mefenamic acid and similarly acting agents as anti-inflammatory agents; however, the only use of prostaglandin (PG) inhibition *in vitro* was not adequately specific.³

After scanning hundreds of fenamates, mefenamic acid and a few other fenamates emerged from clinical trials.¹ One of the most highly cited drugs in the existing scientific and medical literature, fenamates are one of the most highly studied pharmacological agents which are existing currently. Soon after its introduction, mefenamic acid became one of the highly prescribed medications. In the 1990s, it was reported to be among the top three NSAIDs prescribed⁴ and its worldwide use continues to rise.⁵ A study from Malaysia reported that mefenamic acid and diclofenac were amongst the most commonly prescribed NSAIDs.⁶ New basic science has considerably improved the understanding of the biochemistry of mefenamic acid. As well as maintaining its use in traditional settings, there is a tremendous potential for expanding the application of mefenamic acid to niche roles.¹

PHYSIOLOGY OF MEFENAMIC ACID

A wide range of *in vitro* and *in vivo* studies have demonstrated the plethora of physiological activities of mefenamic acid. The diversity of physiological effects of mefenamic acid makes it a unique NSAID that is clinically helpful for its anti-inflammatory, analgesic and antipyretic effects.¹

Action on COX Enzymes

Cyclooxygenase (COX) enzyme is present in two isoforms COX-1 and COX-2. A third distinct variant as COX-3 is a splice variant of COX-1 and has been recently identified in human brain (mainly in the cerebral cortex), spinal cord and heart tissues in abundance.⁷ The primary function is to regulate pain responses and fever, and COX-3 has been postulated to be the site of action of acetaminophen.⁸ COX-1 is variably expressed in most tissues and regulates normal cellular processes. On the other hand, COX-2 is expressed in the brain, kidney, bone and female reproductive system. Its expression increases during the inflammatory state. NSAIDs like mefenamic acid exhibit their primary effect by inhibiting the COX enzyme or prostaglandin H synthase (PGHS), thereby impairing the conversion of arachidonic acid to its metabolites, including PGs, prostacyclin and thromboxane. Even though COX inhibition underlines the beneficial anti-inflammatory, analgesic and antipyretic effects of NSAIDs, simultaneous COX

inhibition in the gastrointestinal mucosa may lead to its irritation and formation of gastric and intestinal ulcers. Hence, it has been suggested that COX-2 selective or preferential NSAIDs may improve effectiveness without inducing considerable gastrointestinal-related side effects.⁹

Mefenamic acid's action in PG synthetase inhibition, both centrally and peripherally, has been affirmed through several studies and is as potent as, or more than, most other NSAIDs. In addition to PG synthesis inhibition what is unique about mefenamic acid is its ability to block the E-type prostanoid (EP) receptors, thereby blocking the pre-formed PGs as well.^{10,11} Mefenamic acid is considered a competitive, time-dependent and reversible inhibitor for COX-1 and COX-2.¹ In a study, it was shown that mefenamic acid is preferential COX-2 and has 12.5-fold selectivity for COX-2 in the blood.⁹

Action on NLRP3 Inflammasome

A key function of a subgroup of NLR proteins is to mediate inflammasome function in the defense of the host. NLR-mediated inflammasome activation is important in host immune response not only to bacteria, fungi, viruses (including COVID-19) and possibly parasites, but also to damage-associated molecular patterns (DAMPs). In addition, these NLRs play a crucial role in modulating immune responses in many metabolic disorders, tumorigenesis and autoimmune disorders. However, a dysregulated activity is associated with a number of inflammatory, immune and metabolic disorders (such as type 2 diabetes mellitus, obesity, atherosclerosis and gouty arthritis).¹² Aberrant activation of NLRP3 inflammasome has fueled the severity of dengue inflammation, febrile convulsions and periodontal inflammation.

Following an infection or injury, the components of inflammasome collect and oligomerize, causing autocleavage of procaspase-1 to its active form. This activation facilitates the conversion of pro-inflammatory cytokines to their active forms (pro-interleukin [IL]-1 β and pro-IL-18 to active form IL-1 β and IL-18), causing an inflammatory response. The inhibition of aberrantly activated NLRP3 inflammasome is an important therapeutic target in inflammatory diseases.¹³

Fenamate NSAIDs (mefenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1 β release by blocking the membrane volume-regulated anion [chloride] channel (VRAC) and volume-modulated transient receptor potential (TRP) channels.¹⁴ These blockades act independently of its COX-mediated anti-inflammatory

activity. It has also been established that there is a synergy between inhibitors in inflammatory pathways to bring about different levels of inhibition and more than observed singly.¹⁵

Antiviral effect

Viruses encode one or more proteases that play crucial roles in either their entry into the host cells or their replication through processing of viral polyproteins. The proteases present in various viruses specifically belong to the family of serine proteases as in hepatitis C virus (HCV), Flavivirus and herpes viruses; the family of cysteine proteases as in adenoviruses (AdVs); or the family of aspartyl protease as in human immunodeficiency virus of type 1 (HIV-1).¹⁶

Mefenamic acid has shown significant activity against viral replication concentration either alone or in combination with the common antiviral drug, ribavirin. Mefenamic acid has demonstrated significant antiviral activity previously against dengue and chikungunya viruses. The study results suggested that the combination of mefenamic acid with ribavirin can be effectively used against other viral infections.¹⁷ In another study, mefenamic acid and doxycycline showed considerable inhibition of DENV2 NS2B-NS3 protease of dengue virus; mefenamic acid showed higher selectivity against dengue virus replication *in vitro* compared to doxycycline. The authors suggested that the antiviral and anti-inflammatory activities of mefenamic acid can be utilized in attenuating the clinical symptoms of dengue infection.¹⁸ In another *in vitro* study, it inhibited the adsorption and/or penetration of encephalomyocarditis virus.¹⁹

The antiviral activity of mefenamic acid can also be helpful in managing COVID-19 along with its action as an antipyretic, especially in the early viremia phase. In one of the literatures, it is indicative that mefenamic acid may inhibit the serine proteases and therefore it can be hypothesized that it may block either the cell entry of the virus or prevent replication by preventing cleaving of the viral polyproteins.²⁰

CLINICAL USES OF MEFENAMIC ACID

Mefenamic acid exhibits anti-inflammatory, analgesic and antipyretic activities and is employed for various clinical uses as depicted in the Box 1.

Antipyretic Activity

Fever is induced by elevation of prostaglandin E2 (PGE2) in the brain and involves PGE2-EP receptor signaling in the hypothalamus, which raises the set point

Box 1. Clinical Uses of Mefenamic Acid

Antipyretic

- Fever of any origin
- COVID-19 (Infective fever and inflammatory fever)

Anti-inflammatory and analgesic action

- Dysmenorrhea
- Postpartum pain
- Menorrhagia
- Menstrual migraine
- Headache
- Musculoskeletal injuries
- Low back pain
- Osteoarthritis
- Rheumatoid arthritis
- Post-COVID myalgia
- Endodontic pain
- Preoperative pain particularly dental procedures
- Postoperative pain

of hypothalamic thermostat for body temperature.²¹ Inflammatory stimuli through activation of COX-2 and microsomal PGE synthase in brain endothelial cells act upon the EP receptor-expressing neurons, resulting in fever.²²

Ideally, the antipyretics act by inhibiting the COX in the brain and hence decrease the PGE2 levels in the hypothalamus.²³ Mefenamic acid is the only NSAID with dual action - central and peripheral. It acts by inhibition of COX-2 in the hypothalamus and leads to effective fever reduction. Additionally, mefenamic acid also acts on the EP receptor, thereby making the preformed PGs ineffective as well.²⁴⁻²⁶

A case series including 71 patients from 3 months to 15 years of age showed that mefenamic acid given in a 4 mg/kg dose possessed optimal antipyretic effect. The antipyretic effect was noted to be 2.5 times that of paracetamol and nearly similar to aminophenazone.²⁷ Mefenamic acid is registered for use in fever from 6 months of age and is an important alternative NSAID to ibuprofen in fever management.²⁸ One of the recent studies indicated that NLRP3 protein was significantly up-regulated in the typical febrile seizure children compared in fever only controls. Increased NLRP3 can mediate IL-1 β secretion that is responsible for the occurrence of febrile seizures (FS).²⁹ The NLRP3 inflammasome inhibitory action of mefenamic acid may attenuate the levels of pro-inflammatory cytokines (IL-1 β). In another prospective study in patients with

fever, mefenamic acid had a faster onset of action and led to a sustained fall in temperature, even at the end of 6 hours, the fall in temperature for mefenamic acid being statistically higher (2.60°F). The study results also showed that mefenamic acid has better efficacy and tolerability than paracetamol and ibuprofen.³⁰

Analgesic and Anti-inflammatory Activity

Inflammation is the immune system's response to infection and injury and PGs play a key role in the generation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue and they contribute to the development of the cardinal signs of acute inflammation.³¹ Arachidonic acid-derived PGs not only contribute to the development of inflammation as intercellular pro-inflammatory mediators, but also promote the excitability of the peripheral somatosensory system, contributing to pain exacerbation.³²

Traditionally, PGs have been viewed as inflammatory mediators connecting innate immunity to phases of acute inflammation with pro-inflammatory cytokines (tumor necrosis factor [TNF]- α and IL-1 β) and lipopolysaccharides known to induce expression of inducible COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1).³³ However, COX-2 and mPGES-1 expression is also observed in chronically inflamed tissues including joints of rheumatoid arthritis patients, colons of patients with inflammatory bowel disease and cancerous tumors and their micro-environment.³⁴ Therefore, PGs appear to play integral roles during both acute inflammation and chronic inflammatory diseases. This PG helps release pro-inflammatory cytokines and chemokines through the EP2 receptors. In humans, PGE2 promotes IL-1 β -dependent production of IL-6, macrophage colony-stimulating factor (M-CSF) and vascular endothelial growth factor (VEGF) from human fibroblasts via EP4 receptors. It also enhances induction of IL-6 and other pro-inflammatory cytokines upon many stimuli in monocytes, macrophages, fibroblasts and airway epithelial cells through both EP2 and EP4 receptors. Besides, IL-6 also up-regulates COX-2 gene expression and increases PGE2 production, working together for normalized production of other inflammatory factors such as matrix metalloproteinase (MMP)-9. PGE2 can also trigger IL-6 production in a paracrine way, creating a vicious cycle.³⁵

Many inflammatory diseases are guided by the pro-inflammatory cytokine IL-1 β . As discussed earlier pro-IL-1 β is the inactive form, which is activated by the protease Caspase-1. Caspase-1 is present as an inactive

precursor, which is activated due to recruitment to a large multiprotein complex called the inflammasome. NLRP3 inflammasome is commonly associated with inflammatory diseases such as atherosclerosis, metabolic diseases¹⁵ and COVID-19.

Considering the strong inflammatory potential of the NLRP3 inflammasome, it is an essential druggable target, and its inhibition can potentially reduce excessive tissue inflammation. Cytokines play a key role in causing inflammation; hence, blocking their effects can be effective in the treatment of rheumatoid arthritis, psoriasis, dysmenorrhea, inflammatory bowel disease and other autoinflammatory diseases.³⁶

When compared to other NSAIDs, mefenamic acid possesses superior anti-inflammatory action. Its anti-inflammatory action is due to the preferential inhibition of the COX-2 enzyme both centrally and peripherally, responsible for converting arachidonic acid to PGs.⁹ Mefenamic acid is the only NSAID that blocks EP receptors to prevent the effects of already released PGE2 (preformed PGE2).^{10,11}

Mefenamic acid inhibits the secretion of IL-1 β by selectively inhibiting the NLRP3 inflammasome through a reversible blockade of volume-regulated anion channels in the plasma membrane and volume-modulated TRP channels.^{14,15}

Mefenamic acid has been frequently used for treating the pain of dysmenorrhea in the short-term and also mild-to-moderate pain, including headache, dental pain, postoperative and postpartum pain.³⁷

NSAIDs are used as first-line treatment of primary dysmenorrhea; however, there is no optimal clinical choice among NSAIDs. In a network meta-analysis of randomized controlled trials, it was found that mefenamic acid showed superior pain relief compared with nimesulide, rofecoxib and valdecoxib.³⁸ In addition, several studies have demonstrated that when compared with placebo, mefenamic acid is undoubtedly superior in relieving dysmenorrhea.¹

Earlier trials showed that fenamates, including mefenamic acid, were superior to ibuprofen, naproxen and indomethacin. Several other studies showed that mefenamic acid was equivalent to ibuprofen, naproxen, ketoprofen, piroxicam and meloxicam. Mefenamic acid was also found to be superior to the combination of dextropropoxyphene and paracetamol. Mefenamic acid plays an effective role in reducing pain and blocking increased uterine contractility stimulated by PG-endoperoxide analogs.¹

In guidelines by the American Academy of Neurology and the American Headache Society, mefenamic acid was included as one of the possible effective treatments of migraine, which may also be considered for migraine prevention.³⁹

Mefenamic acid has been frequently used to treat dysmenorrhea and mild-to-moderate pain, including headache, dental pain, postoperative and postpartum pain. A study showed that oral mefenamic acid 500 mg was effective in treating moderate-to-severe acute postoperative and postpartum pain.³⁷ A study has demonstrated that mefenamic acid is significantly superior to placebo in treating acute menstrual migraine. The study results concluded that mefenamic acid is safe and effective for the treatment of acute menstrual migraine.⁴⁰

In a systematic review, mefenamic acid has been shown to offer a good level of pain relief, reducing the pain by 50% in those suffering from moderate-to-severe postoperative pain following a single dose of mefenamic acid 500 mg. The pain relief experienced by the study participants was comparable with paracetamol 1000 mg.³⁷

Mefenamic acid helps in reducing pain in case of musculoskeletal injuries being treated in the ambulatory emergency setting. The relief has been reported to be analogous to other NSAIDs, paracetamol and propoxyphene/paracetamol, especially in patients with Colles' fracture. Mefenamic acid can also be given in case of soft tissue injuries. A physicians' and patients' pain rating analysis revealed that patients with acute back pain in ambulatory settings benefit from mefenamic acid.^{41,42} It was found that mefenamic acid was more commonly chosen in an evaluation than other NSAIDs and drugs for this purpose.⁴²

Mefenamic acid is reported to be beneficial in patients who have rheumatoid arthritis. Clinical studies have demonstrated that in total doses of 1 and 1.5 g/day, mefenamic acid leads to an effect equivalent to many other NSAIDs. Some studies have also suggested that mefenamic acid can have equivalent or superior activity than other NSAIDs for chronic osteoarthritis, including the elderly.¹ It has been proven in earlier studies that compared with paracetamol, codeine and dihydrocodeine, mefenamic acid reduces not only pain but also inflammatory swelling.⁴³

In a double-blind, randomized single-dose study of the analgesic effects of mefenamic acid alone and in combination with aspirin, it was seen that while aspirin and the mefenamic acid combination was more effective

than either of the drugs used alone, mefenamic acid used exclusively was also equally effective for most of the analgesic variable.⁴⁴ Furthermore, when used in a dose of 500 mg administered thrice daily, the analgesic activity of mefenamic acid was comparable to 2.4 g aspirin given daily.⁴⁵

In the first-ever study in humans, it has also been shown that mefenamic acid may be used as a neuroprotector. The anti-inflammatory activity of mefenamic acid, particularly targeting the NLRP3 inflammasome pathway, improved cognitive impairment and reversed memory loss and brain inflammation. The neuroprotection was seen due to the reduced free radical production, nitric oxide and cytochrome C release, and up-regulation of the anti-apoptotic protein expression, B-cell lymphoma-extra large (Bcl-xL) protein. Besides, the study did not show any serious adverse events associated with 6 months use of mefenamic acid.⁴⁶

In the inflammatory conditions where aberrant activation of NLRP3 inflammasome has been implied, the inhibitory action of mefenamic acid on the COX enzymes and NLRP3 inflammasome may have synergistic action and effectively reduce the inflammation.

THE CASE OF MEFENAMIC ACID BEING REPURPOSED IN COVID-19

Most of the drugs used in COVID-19 management have been repurposed such as hydroxychloroquine, ivermectin, favipiravir and remdesivir.⁴⁷⁻⁵² Similarly, mefenamic acid with its antipyretic, anti-inflammatory, analgesic and antiviral activity is also considered to be a potential therapy in the management of COVID-19.

In COVID-19 infection, lysosomal disruption and ion-redistribution in the intracellular environment activate the innate immune signalling receptor NLRP3 inflammasome. This leads to the production of inflammatory cytokines such as IL-1 β , IL-6 and TNF- α , causing tissue inflammation during a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Considering the triggering inflammatory response to infection, the NLRP3 inflammasome may be a potential drug target in the treatment of COVID-19.³⁶

Studies have shown that fenamates (mefenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1 β release through the inhibition of the membrane VRAC, independent of its COX-mediated anti-inflammatory activity.¹⁵

In a series of 5 cases, it was seen that early initiation of treatment with mefenamic acid offered symptomatic

relief to the patients, who were not hypoxic, in reducing fever. In addition, the use of mefenamic acid led to reduced C-reactive protein (CRP) values, which can also prevent cytokine storm, reflecting the significant anti-inflammatory activity of mefenamic acid in COVID-19 patients. It has also been suggested that mefenamic acid may be used in post-COVID myalgia until the CRP level falls under one.⁵³

In a review on repurposing mefenamic acid in the management of COVID-19, the group of experts recommended that mefenamic acid could be safely used from the first day of infection. It can also be used at any stage of COVID-19 for its antipyretic, analgesic and anti-inflammatory activity.³⁵ As evident from various studies, the effect of different NSAIDs, including mefenamic acid, on different aspects of the immunopathogenesis of COVID-19 is shown in Table 1.^{35,54-57} Various studies have shown the antiviral activity of mefenamic acid. Combining the antiviral and anti-inflammatory effects of mefenamic acid effectively improved the pathological signs of inflammatory diseases like COVID-19.

ADVERSE EFFECTS

Considering the safety profile, mefenamic acid possessed a significantly lower risk of adverse events, while indomethacin demonstrated a higher risk than any other NSAID. In a recent network analysis, mefenamic acid and tiaprofenic acid were considered the safest NSAIDs compared to nimesulide, rofecoxib, valdecoxib, aspirin, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen and piroxicam.³⁸

Minor gastrointestinal symptoms are also linked with the use of some NSAIDs, including mefenamic acid. In a study on pain relief in primary dysmenorrhea, mefenamic acid was considered one of the safest NSAID drugs in terms of safety outcome, while indomethacin was the worst one which was more likely to cause mild

gastrointestinal discomfort. In the same study, naproxen did not show any superiority in terms of efficacy or safety.³⁸

There are also reports of a transient rise in liver function tests resulting from mefenamic acid overdose. In acute overdose, renal impairment has also been found in patients with underlying renal and cardiovascular disease individuals. Some reports have also suggested prolongation of prothrombin time with the use of mefenamic acid.⁵⁸

A study conducted on the long-term use of mefenamic acid in women with menorrhagia demonstrated that long-term use (6-9 months and 12-15 months) was not only beneficial in reducing pain, but the side effects also reduced over the duration of treatment. The gastrointestinal side effects such as nausea, diarrhea also reduced with time, while a significant increase in serum ferritin was noted between admission and completion of the follow-up trial.¹⁰

Mefenamic acid is contraindicated during third trimester of pregnancy, individuals with risk or past history of gastrointestinal bleeding and in severe hepatic/renal impaired patients. According to the official journal of the American Academy of Pediatrics (AAP), mefenamic acid is compatible with breastfeeding.⁵⁹

FUTURE RECOMMENDATIONS

Hyperinflammatory response of the host has been noted to be a common feature in different viral infections, including dengue and SARS-CoV-2. It also occurs in cases where low-titer antibodies to the virus enhance the infection in immune cells. This occurs via a process called antibody-dependent enhancement (ADE), which can occur after vaccination or secondary infections with other corona, Ebola and dengue viruses.⁶⁰

It remains to be explored through clinical studies whether NSAIDs like mefenamic acid with potent

Table 1. Action of Different NSAIDs on the Immunopathogenesis of COVID-19^{35,54-57}

Cytokine	NLRP3	IL-1 β	IL-6	TNF- α	Serine protease
Acetofenac	x	↓	↓	↓	x
Diclofenac	x	↓	↓	↓	x
Ibuprofen	x	↑	.	↑	x
Mefenamic acid	√	↓ ++	↓ +++	↓ ++	√
Nimesulide	x	↓	↓ +	↓	x
Paracetamol	x		↔	↓	x

antipyretic, anti-inflammatory and antiviral activities can play a significant role in combating hyperinflammatory response due to ADE in vaccinated individuals or those with secondary viral infections.

CONCLUSION

Considering the wide range of physiological actions of mefenamic acid, there are several avenues where it can be used effectively. Analgesic, anti-inflammatory and antipyretic effects of mefenamic acid have been utilized in the clinical use of the drug. Mefenamic acid has been a promising agent in treating several inflammatory conditions, including fever, inflammatory diseases such as arthritis, pain relief in dysmenorrhea and myalgia. It continues to evolve persistently for other clinical usages. During the pandemic, mefenamic acid emerged as an efficient means of managing fever, inflammation and post-COVID symptoms of myalgia and pain. It has an established efficacy and safety profile over the long-term and can also be used for up to a year without developing any serious adverse events.

Studies have established mefenamic acid as one of the safest NSAIDs. It is registered to be used from 6 months of age as an effective antipyretic and may be safely used for different clinical purposes across all the age groups.

In the ongoing COVID-19 pandemic, one of the successful approaches for accelerating the identification of treatment options is repurposing of the existing drugs. In this context, mefenamic acid has been successfully repurposed off-label as an adjuvant in the management of COVID-19. While maintaining the use of mefenamic acid in conventional settings, there is also a remarkable potential for expanding its use to niche roles.

Going ahead, the authors recommend exploring further role of mefenamic acid in various inflammatory conditions especially where NLRP3 inflammasome is implied in its pathophysiology.

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Clinical, Laboratory and Neuroimaging Profile of Children with Infantile Tremor Syndrome at a Tertiary Care Center

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ABSTRACT

Introduction: Infantile tremor syndrome (ITS) is characterized by coarse tremors, anemia, pigmentary skin changes, regression of developmental milestones, muscle hypotonia and multiple micronutrient deficiencies. We studied clinical, laboratory and neuroimaging profile of children with ITS. **Material and methods:** This hospital-based prospective observational study was conducted in the Dept. of Pediatrics, SMS Medical College, Jaipur, Rajasthan. Fifty cases of pre-ITS or ITS, 4 months to 3 years of age, admitted in the department were included in the study and assessed at the time of admission in hospital and at follow-up after 3 months of discharge with detailed clinical, hematological and neuroimaging examination. **Results:** We noted a female preponderance. About 96% children were from rural background, 88% from poor socioeconomic status and 12% children were from lower middle socioeconomic status. Eighteen (36%) children presented with leukocytosis. Only 24 (48%) children had normal serum iron level, and 24 (48%) children had normal serum vitamin B12 at presentation. Six (12%) children had decreased level of serum folate (<3 ng/dL). All the parameters improved at follow-up after 3 months. Magnetic resonance imaging (MRI) brain was normal in 10% children, while MRI brain in 32 (64%) children revealed cortical atrophy. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRIs showed normal findings when compared with previous MRI done on admission but 7 MRIs out of 24 showed improvement on follow-up, compared to the MRI done on admission; however, changes in MRI were still seen and had not completely resolved. **Conclusions:** The encouraging results of nutritional rehabilitation suggest that supplementing mother with vitamin B12 during pregnancy or fortifying complementary feeds with vitamin B12 may be considered. As the infants with vitamin B12 deficiency show neuroregression and features similar to ITS and the fact that vitamin B12 is involved in evolution of DNA and myelinating changes, vitamin B12 deficiency may be implicated as etiology.

Keywords: Infantile tremor, MRI brain, nutrition

Infantile tremor syndrome (ITS) is marked by coarse tremors, anemia, pigmentary skin changes, regression of developmental milestones and muscle hypotonia, in a plump looking child. ITS usually affects infants aged 6-24 months, though infants younger or older than this have also been reported to be affected, with male preponderance in the majority of the studies.

While the exact incidence of ITS is not known, hospital statistics indicate that around 0.77-2.5% of the pediatric ward admissions are attributed to this disorder. Besides anemia, infants with ITS often present with multiple micronutrient deficiencies in the form of angular cheilitis, stomatitis and glossitis. Rickets, scurvy, edema and vitamin A deficiency have also been reported. Most researchers agree that infants with ITS are malnourished.

Non-specific changes have been noted on neuroimaging in ITS patients in the form of cerebral atrophy. However, these changes are also noted in the cases of malnutrition and after certain viral infections of the central nervous system (CNS). Earlier, pneumoencephalography has been associated with signs of ventricular dilatation and cortical atrophy in patients with ITS. Cranial neuroimaging is an important component of investigations to determine the etiological correlation in the differential diagnosis of conditions associated with

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tremors. The present study describes clinical, laboratory and neuroimaging profile of children with ITS at a tertiary care center.

MATERIAL AND METHODS

This hospital-based prospective observational study was conducted in the Dept. of Pediatrics, SMS Medical College, Jaipur, Rajasthan, from June 2017 to May 2018, after requisite clearance from research review board of the institute. Sample size was calculated as 95% confidence level, Alpha Error of 0.05 assuming 53.33% tremors among the suspected cases of ITS, at an absolute allowable error in the tremors of the suspected cases of ITS. The required sample size was 50 cases of pre-ITS or ITS. All children >4 months and <3 years of age, presenting with tremors, skin pigmentary changes, anemia and mental developmental delay with brown scanty scalp hair admitted in the department were included in the study and assessed at the time of admission in hospital and at follow-up after 3 months of discharge with detailed clinical, hematological and neuroimaging examination. We supplemented all the nutrients including calcium, folic acid, vitamin B12, iron, multivitamin, zinc, phosphorus, magnesium, potassium and proper food supplementary advice was given at the time of discharge. At 3-month follow-up, 26 patients came to us again and we assessed them clinically, hematologically and developmentally and neurologically. We found that almost all cases of ITS/pre-ITS which were documented 3 months back, showed drastic improvement in all four domains. Developmental assessment was done at the CDC center in Sir Padampat Mother and Child Health Institute (SPMCHI), Jaipur using DASII (Developmental Assessment Scale for Indian Infants) method. Children with negative consent and those with other diagnoses, perinatal insult like hypoxic ischemic encephalopathy, neonatal jaundice, etc. and CNS infections like TORCH (Toxoplasmosis, Other agents, Rubella, Cytomegalovirus and Herpes simplex virus), tuberculous meningitis (TBM), pyomeningitis, etc., were excluded from the study. Data were analyzed statistically.

OBSERVATIONS AND RESULTS

Socio-demographic Profile

In our study, 44% (22) children were in 9-12 months age group, 30% (15) children were in 12-15 months age group and 26% (13) children were in 6-9 months age group. Forty-four percent (22) children were male and 56% (28) children were female. Ninety-six percent (48)

children were from rural area and 4% (2) children were from urban area. Additionally, 96% (48) children were Hindu and 4% (2) were Muslim. Ninety-six percent (48) children were from vegetarian family and 4% (2) were from nonvegetarian family. Furthermore, 88% (44) children were from poor socioeconomic status and 12% (6) children were from lower middle socioeconomic status, according to Kuppuswamy's scale.

Clinical Profile of ITS/Pre-ITS Children on Admission

All children presented with pallor, hair color change and dark pigmentation of skin. Eighteen (36%) children presented with leukocytosis at the time of admission and at follow-up at 3 months, 2 (4%) children had leukocytosis (Table 1).

Twenty-five (50%) children presented with consolidation in chest X-ray at the time of admission and at follow-up at 3 months, none had consolidation. Ten (20%) children presented with nonsterile urine culture at the time of admission while all children had sterile urine culture at follow-up. Two (4%) children had nonsterile blood culture at the time of admission and at follow-up, all had sterile blood culture. Overall, 94% children had associated comorbid illness, like acute upper respiratory tract infection (URTI) (16%), pneumonia (50%), urinary tract infection (UTI) (20%), sepsis (4%) and persistent diarrhea (4%) (Fig. 1). All patients were developmentally delayed, in which 80% (40) patients were with regressed milestone and 20% (10) patients were with delayed milestone. In all, 96% (48) patients had apathetic look in our study.

No children had normal weight at the time of admission and at 3-month follow-up, 38% children had normal body weight according to the World Health Organization (WHO) growth chart (Table 2).

Table 1. Clinical Symptoms of ITS/Pre-ITS Children on Admission

Symptoms	No. of children	Percentage (%)
Pallor	50	100
Hair color change	50	100
Dark pigmentation of skin	50	100
Associated comorbid illness	47	94
Regressed milestone	40	80
Delayed milestone	10	20
Apathetic look	48	96

Signs of ITS/Pre-ITS on Admission

Hundred percent children had developmental delay, wherein 10 (20%) patients were actually developmentally delayed since birth and 40 (80%) patients were developmentally regressed; they were normal at the

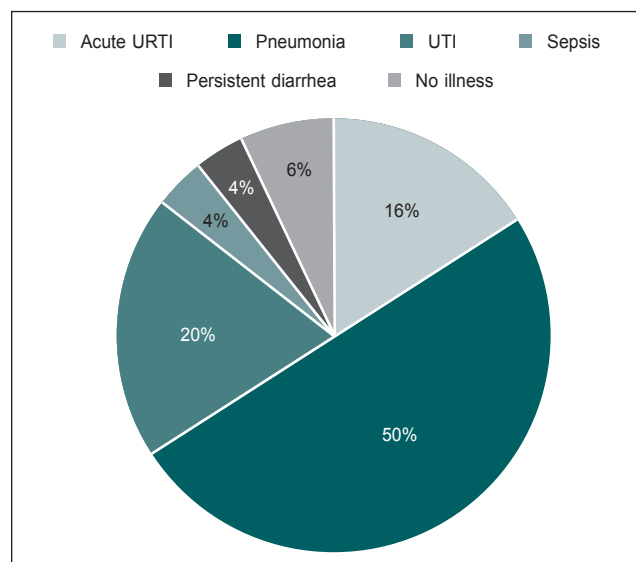


Figure 1 Associated comorbid illness in ITS and pre-ITS patients (n = 50).

time of birth to 3-4 months, and after that, they show development delay. Anemia and dark pigmentation of skin were present in 100% patients. Overall, 38% children presented without tremor and 62% presented with tremor (Table 3).

Hematological Profile

None of the children presented with hemoglobin (Hb) level >11 g/dL at the time of admission and at follow-up at 3 months, 53.85% children had Hb level >11 g/dL. Two (4%) children had normochromic, normocytic peripheral blood film (PBF) at the time of admission and at follow-up, 54% children had normochromic, normocytic PBF. Twenty-four (48%) children presented with normal serum iron level at the time of admission and at follow-up, 92% children had normal serum iron level. Only 72% children presented with normal total iron-binding capacity (TIBC) level at the time of admission and at follow-up, 100% children had normal TIBC level.

Serum vitamin B12 levels at the time of admission and after follow-up are depicted in Table 4.

Six (12%) children revealed decreased level of serum folate <3 ng/dL. On follow-up after 3 months, 100% children had normal serum folate level.

Table 2. Weight for Age (According to WHO Growth Chart)

Weight for age (according to WHO growth chart)	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Mean weight or more	0	0	10	38.46
B/w Mean & 1 SD	3	6	14	53.85
B/w 1 SD & 2 SD	7	14	2	7.69
B/w 2 SD & 3 SD	12	24		
B/w > 3 SD	28	56		
Total	50	100.00	26	100.00

Table 3. Signs of ITS/Pre-ITS on Admission

Sign	No. of children	Percentage (%)
Tremors absent	19	38
Tremors present	31	62
Developmental delay	10	20
Developmental regression	40	80
Anemia	50	100
Dark skin pigmentation	50	100

Table 4. Serum Vitamin B12 Levels at the Time of Admission and at Follow-up

Serum vitamin B12 (pg/dL)	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
<211	26	52	0	00
211-911	24	48	26	100
>911	0	0	0	0
Total	50	100.00	26	100.00

Table 5. MRI Brain at Presentation and Follow-up Visit

MRI	Before treatment (n = 50)		Follow-up (n = 26)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Normal	5	10	17	70
Cortical atrophy	32	64		
Ventricular dilatation	10	20		
Thinning of corpus callosum	6	12		
Subdural effusion	6	12		
Prominence of sylvian sulcus	12	24		
Diffuse dilatation of sulci	19	38		
Generalized atrophy of grey matter	4	8		
Miscellaneous	4	8		

Neuroimaging Profile

Eighty-two percent children had normal cranial USG at the time of admission and at 3 months follow-up, 100% children had normal cranial USG.

In our study, 5 (10%) children had normal MRI of brain. Thirty-two (64%) children had cortical atrophy at the time of admission, 10 (20%) children presented with ventricular dilatation and thinning of corpus callosum was revealed in 6 (12%) MRI of brain. Prominence of sylvian sulcus was seen in 12 (24%) children, diffuse dilatation of sulci was seen in 19 (38%) children and generalized atrophy of grey matter was seen in 4 (8%); remaining miscellaneous changes like cerebellar atrophy, delayed myelination (hyperintensities in cortical areas) were seen in 4 (8%) children at the time of admission (Table 5).

Two out of 26 attendants refused for repeat MRI of brain on follow-up. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRI showed normal finding on follow-up and 7 showed improvement in MRI changes that were

noted previously on admission but had not completely resolved till date of follow-up.

In our study, motor quotient at 50% pass level (according to DASII developmental scale) was 37.46 ± 5.89 and at 3-month follow-up, motor quotient at 50% pass level was 71.38 ± 5.72 . The difference between before and after treatment value was found to be statistically significant. The mental quotient at 50% pass level was 38.52 ± 4.61 and at follow-up, mental quotient at 50% pass level (according to DASII developmental scale) was 73.23 ± 5.50 . The difference between before and after treatment value was again statistically significant.

DISCUSSION

In our study, 44% children presented in 9-12 months age group, 44% children were male and 56% children were female. All children had abnormal weight. In a study conducted by Parsawala et al, most of the patients (93.3%) were found to have some degree of protein energy malnutrition (PEM), with maximum having Grade II.

No child had Hb level >11 g/dL at the time of admission and at follow-up, Hb levels improved in 53.85% children. Only 24 (48%) children had normal serum iron level at the time of admission and at follow-up, 92.31% children had normal serum iron level. Overall, 72% children had normal TIBC level at the time of admission while all children had normal TIBC level at follow-up. Twenty-four (48%) children had normal serum vitamin B12 at the time of admission and at follow-up, 100% children had normal level. Six (12%) children had decreased level of serum folate <3 ng/dL, which improved at follow-up in all children.

In our study, MRI brain was normal in 10% children, while in 32 (64%) children, it revealed cortical atrophy. Mathur et al have suggested that these anatomical changes might be attributed to PEM. A case report of ITS reported computerized tomography (CT) scan of the brain showing cerebral atrophy with thinning of corpus callosum. A study on patients with essential tremors (ETs) noted that high resolution proton density and T2-weighted MRI images among 12 patients and 15 controls did not show any structural abnormalities of the brain. Various degrees of cerebral atrophy have been evaluated in children having CNS manifestations of PEM.

A study conducted by Kumar et al found cerebral atrophy in 7 patients of ITS (53.8%), subdural hygroma in 2 patients while rest of the 4 patients were normal. In a study by Gehlot et al, among ITS cases with severe wasting, 3 out of 4 had cerebral atrophy. All 3 children with moderate wasting had signs of cerebral atrophy. There was evidence of cerebral atrophy in all children with stunting and also in children with normal height for age and sex. Six out of 10 patients had mild-to-moderate ventricular dilatation and most patients (9/10) had sylvian sulcus prominence. Ventricular dilatation and prominence of sylvian sulcus were correlated with the grades of cerebral atrophy in all patients.

In our study, 10 (20%) children presented with ventricular dilatation, 6 (12%) children each presented with thinning of corpus callosum and subdural effusion at the time of admission. After 3 months, 26 children came for follow-up. Two out of 26 attendants refused for repeat MRI of brain on follow-up. In 24 (92% of 26) follow-up MRI brain, 17 (70%) MRIs showed normal findings as compared to previous MRI done on admission, but 7 MRIs out of 24 showed improvement on follow-up as compared to previous MRI done at admission, but changes in MRI of brain were still seen and had not completely resolved.

A study conducted by Gehlot et al noted that on cranial neuroimaging, there was non-specific cerebral atrophy of different grades in all cases except one while cerebellar atrophy was noted in 1 case of ITS. Corpus callosum thickness was reduced in 6 patients while 9 had prominence of sylvian sulcus.

Motor quotient and mental quotient at 50% pass level difference between before and after treatment was found statistically significant.

In a case series of childhood head tremors, MRI showed no abnormal findings. Hypomyelination disorders are associated with evidence of cerebral and cerebellar atrophy and little or no myelin in the cerebral white matter on MRI scans of most adolescents and adults. The infantile form of Pelizaeus-Merzbacher disease (PMD) that presents with head tremors, is associated with mild-to-moderate brain atrophy. There is little MRI data on the patients clinically diagnosed as ITS.

A study conducted by Gupta et al found that MRI changes in ITS/pre-ITS patients showed improvement after nutritional rehabilitation on follow-up even 2 months later. As persisting neurodisability is a concern, it should be prevented rather than treated.

FUTURE RECOMMENDATIONS

The encouraging results of nutritional rehabilitation suggest that supplementing the mother with vitamin B12 during pregnancy or fortifying complementary feeds with vitamin B12 may be considered because vitamin B12 seems to be the etiological factor in ITS as per studies. As the infants with vitamin B12 deficiency show neuroregression and features similar to ITS and the fact that vitamin B12 is involved in evolution of DNA and myelinating changes, vitamin B12 deficiency may be implicated as the possible etiology.

In infants, vitamin B12 deficiency is tied to demyelination and brain atrophy. Therefore, retardation of myelination of the brain in infants results in delay in acquiring cognitive skills and regression of cognitive skills. The most common neuroimaging finding in all studies correlate with cortical atrophy. Some reports specifically indicate demyelinating changes. While neurological injury is classically described as irreversible, patients of stroke and other injuries usually recover with gliosis or porencephalic cyst, and patients of ITS show complete recovery. The cortical atrophy heal or recover without scarring.

Patients of ITS tend to have persisting neurodisability - their IQ is on lower side in comparison with others of the

same age, while some may attain normal development few months after treatment. The degree of improvement may be associated with the time of presentation. As the brain is still a developing organ and myelination continues, till 2 years of age, early intervention results in less damage to the brain and there are lesser odds of neurodisability. Early diagnosis and treatment are essential.

CONCLUSION

Our finding of complete resolution of MRI findings of cortical atrophy, ventricular dilatation, demyelination, increased subarachnoid space, etc., would suggest the possibility of near complete reversibility of the neurological abnormalities and support recommendation of vigorous attempts for rehabilitation of the patients.

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Study Shows Signs of Brain Inflammation in People Who Died of COVID

A new study has noted signs of inflammation and neurodegeneration in the brains of people who succumbed to COVID-19, similar to those seen in people who die of Alzheimer's and Parkinson's disease.

The findings from the study may help explain the reason behind so many COVID-19 patients reporting neurological problems. The complaints tend to increase with more severe COVID-19 and can continue as a part of long COVID. Close to one-third of patients hospitalized for COVID-19 have symptoms like forgetfulness, difficulty concentrating and depression. The researchers in the present study did not find any signs of SARS-CoV-2 in brain tissue that they obtained from 8 patients who died of the disease. Brain samples obtained from 14 individuals who died of other causes served as controls. The study is published in the journal *Nature...* (*ET Healthworld – PTI*)

Synchronous Primary Malignancy in Head and Neck

SPS YADAV*, J SINGH†, JS GULIA‡, NEERAJ AGGARWAL‡

ABSTRACT

Advances in the management of squamous cell carcinomas of the head and neck mucosal sites have improved disease control rates and have translated into improved disease-specific survival rates. However, synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites occur in a significant proportion of patients and it may be partially responsible for failure to improve overall survival rates. Authors present one such case of synchronous primary malignancy.

Keywords: Squamous cell carcinoma, synchronous primary tumor, metachronous carcinoma, head and neck cancer

The association of synchronous primary tumors in the aerodigestive tract is known well and has been explained by field cancerization. The mucous epithelium of the head and neck is exposed to common carcinogens, resulting in multiple carcinomas. Epidemiologic data attribute tobacco as a leading carcinogen and alcohol to promote carcinogenesis. The second primary lesion is either detected along with the primary lesion, i.e., synchronous, or after some time, i.e., metachronous. Among patients with carcinomas of mucosa of the head and neck, the rates of synchronous and metachronous carcinomas have been reported to range between 8% and 21% in some studies. Synchronous multiple primary cancers in the head and neck, and the esophagus region confound the clinicians about the favorable treatment options for each tumor and have an adverse impact on the survival and quality of life of the patients.

CASE REPORT

A 46-year-old male patient presented with complaint of swelling on both sides of neck. He had no other

complaints, but on interrogation, he revealed history of difficulty in deglutition, excessive salivation and referred ear pain on left side. On examination, he had swelling in left submandibular area (Fig. 1) and on right side, in lower one-third of neck. Both the swellings were more than 6 cm in size, firm to hard in consistency, nonfluctuant, nontender and nonmobile. Further examination revealed indurated growth in left tonsil and right base of tongue. Biopsy and histopathological examination from both the sites revealed squamous cell carcinoma. Fine needle aspiration cytology (FNAC) of both neck swellings revealed metastatic secondaries. On clinical assessment, patient was classified at stage IV taking the growth individually or combined. He was inoperable so referred to radiotherapy department. However, when the prognosis was explained, patient refused to undergo radiotherapy and left the hospital on risk bond.

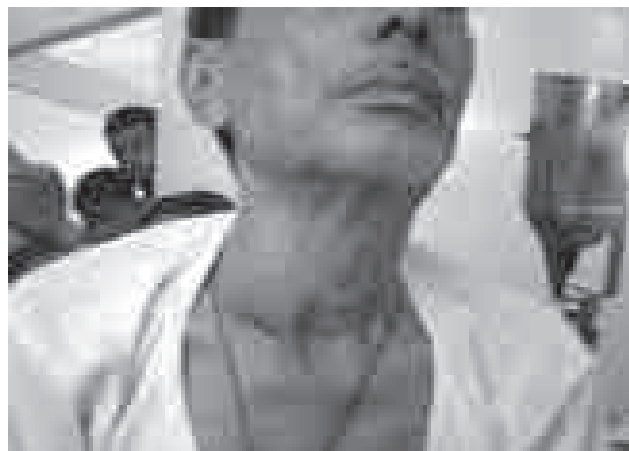


Figure 1 Right neck swelling.

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DISCUSSION

Billroth first introduced the concept of multiple cancers in 1889. Warren and Gates later outlined the criteria to classify multiple neoplasms. Moertel further defined the criteria for differentiating multiple neoplasms from multicentric neoplasms.

Slaughter and colleagues described “field cancerization”, which refers to continuous exposure of the upper aerodigestive tract to an unknown carcinogen, in order to define carcinogenesis of multiple neoplasms in the upper aerodigestive tract.

Tobacco and alcohol have been described as carcinogens involved in field cancerization of the upper aerodigestive tract epithelium. They give rise to marked genetic changes responsible for extensive histologic changes eventually leading to in synchronous and metachronous neoplasms.

Among patients with carcinomas of the mucosal sites of head and neck region, the rates of developing synchronous and metachronous carcinomas of the head and neck mucosal sites correspond to the initial head and neck mucosal sites.

The survival rates and control of disease following synchronous and metachronous carcinomas of the head and neck mucosal sites are driven by the involved sites and extent of disease. Metachronous carcinomas of the lung and thoracic esophagus have been linked with advanced disease, and correlate with worse disease control and survival rates. On the other hand, metachronous carcinomas of the head and neck mucosal sites, especially the oral cavity, have better disease control and survival rates if limited disease is detected early.

Development of synchronous and metachronous squamous cell carcinomas of head and neck mucosal sites could partly be accountable for the failure improving the survival rates in head and neck cancers. Although some head and neck cancers, like nasopharyngeal carcinoma, are known for bilateral lymph node metastasis, especially in late stage; however, in such cases, there has to be a thorough evaluation in order to exclude another synchronous primary malignancy, as in present case. Rigorous follow-up is indicated after treatment of the initial cancer so that second metachronous primary cancers can be detected while it is still limited and treated with a high likelihood of cure.

CONCLUSION

One should meticulously examine the aerodigestive tract in cases of head and neck cancer patients to

detect and treat synchronous primary to avoid disastrous outcome.

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Continued on Page 134...

Lateral Cervical Cyst: A Case Report

SUDHAKAR VAIDYA*, RS PAGARE†, VK SHARMA*

ABSTRACT

Cystic degeneration of cervical lymph nodes is the most accepted theory for occurrence of lateral cervical cyst. It is commonly found in the anterior triangle of the neck, anterior to the upper third of the sternocleidomastoid. Clinical examination, imaging modalities, such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), and fine needle aspiration cytology (FNAC), are useful investigations to establish the diagnosis. Surgical excision of these lesions is reasoned curative in most of the cases. Authors report a case of lateral cervical cyst which was successfully operated.

Keywords: Lateral cervical cyst, branchial cleft cyst, lymphoepithelial cyst

The cervical lymphoepithelial or branchial cleft cyst is a developmental cyst. The pathogenesis for this cyst is not well-understood.¹ Hunczovsky in 1785 gave the first account of cysts in the lateral part of neck. Four key theories have been described in the literature to ascertain their etiology.² Ascherson (1832) described a “branchial theory” which suggested that the cysts occurred due to incomplete obliteration of branchial cleft mucosa, which remained in a dormant state until stimulated later in life, when it starts growing. His, in 1886, proposed the “precervical sinus theory” and said that these cysts were related to the cervical sinus and not the pharyngeal clefts or pouches. Wenglowski, in 1912, suggested that the lateral cervical cysts originated from the third pharyngeal pouch (thymopharyngeal duct theory). During the 19th century, some investigators found an association between lateral cervical cysts and lymphoid tissue (Lucke, 1861). In 1848, Luschka pointed that the formation of lateral cervical cysts was driven by cystic degeneration of cervical lymph nodes. It was only after King (1949) assessed the histology of a large number of lateral cervical cysts and noted that they originate from cystic transformation of cervical lymph nodes that the

“lymph node theory” gained significance.³ Evidence confirming the lymph node theory was provided by Bhaskar and Bernier, who reviewed histopathology of 468 cysts, out of which 452 cysts (96%) were found to be composed of a wall of lymphoid tissue lined with squamous or columnar cells.⁴ Due to a difference in the position, King suggested that any cyst arising outside the midline, with the histological features as stated above should be regarded as a lymphoepithelial or a branchial cyst.^{2,3} While both the branchial cysts and fistulas have been regarded as having branchial origin, now it is believed that branchial cysts have a nonbranchial origin.

CASE REPORT

A 25-year-old woman attended ENT OPD of our medical college and hospital with history of a painless, movable, firm mass in the right side of neck, which had been present for the past 6 months, and was gradually increasing in size. Local clinical examination revealed a solitary, diffuse, nontender cystic swelling of about 5 × 3 cm, on the right side of the neck, just anterior to sternocleidomastoid muscle (Fig. 1). The swelling was nonpulsatile. The carotid pulsations were normal. Ultrasonography showed a cystic mass with smooth margins, just behind the right submandibular salivary gland and anterior to the jugular vein. Thyroid gland was normal and there was no evidence of any other mass (Fig. 2). On fine needle aspiration cytology (FNAC) smears from aspirated thick, yellow-colored material revealed bloody to fatty background and many anucleate squames. Squamous epithelial cells of varying maturity were also seen in the aspirated fluid.

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Figure 1 Swelling on the right side of the neck.

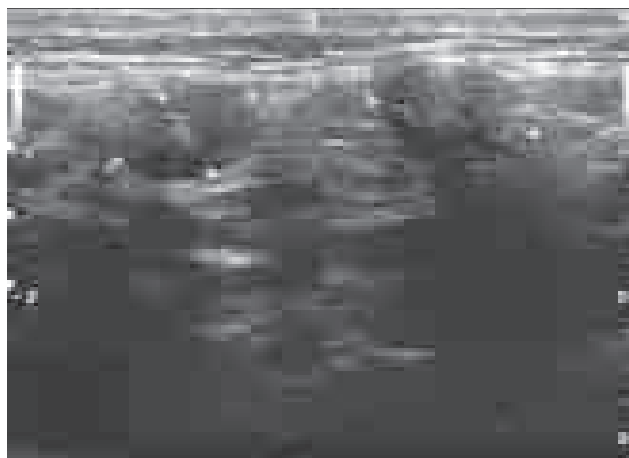


Figure 2 Ultrasonography of the cyst.

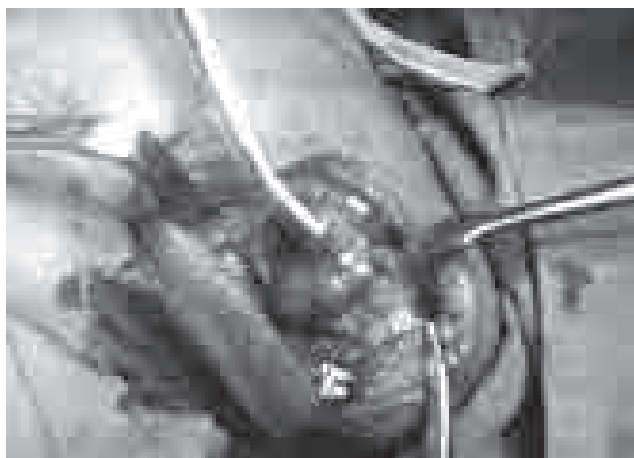


Figure 3 Intraoperative image.



Figure 4 Cyst excised *in toto*.

The patient was taken for excision of the mass under general anesthesia with a provisional diagnosis of lateral cervical cyst. A lateral cervical crease incision was made 2 cm below the lower border of mandible and the neck was explored. The sternocleidomastoid muscle was identified and retracted backwards. A thick walled cyst was found anterior to sternocleidomastoid, posterior to submandibular gland and below the mandible. The investing layer of deep fascia was opened and cyst was dissected from surrounding structures by fine scissors (Fig. 3). No tract or cord was found connecting the cyst to the skin or pharynx. The carotid and jugular vessels were found to be normal. The cyst was excised *in toto* and sent for histopathology (Fig. 4). The wound was closed after introducing minivac drain. Postoperative period was uneventful, the drain was removed after 48 hours and stitches were removed after 7 days. On histopathological examination, the wall of the cyst was found to be composed of stratified squamous epithelium with underlying lymphoid tissue aggregates. Patient is doing well 3 months after excision of the cyst.

DISCUSSION

Lateral epithelial cysts are more prevalent among females and usually occur in the 2nd or 3rd decade of life.² These cysts are most often observed in the anterior triangle of the neck, anterior to the upper third of the sternocleidomastoid. However, they have rarely been reported in the posterior triangle of the neck as well.⁵ Differential diagnosis for this cyst includes lymphangioma (cystic hygroma, lymphatic malformations), glandular cysts, lymph nodes, ranulas, dermoid cysts, laryngoceles, thyroglossal duct cysts, lipomas, hemangiomas (venous malformations) and paragangliomas.

Preoperative diagnosis is a challenge. Clinical examination, imaging modalities, such as (ultrasonography, computed tomography [CT] and magnetic resonance imaging [MRI]), and FNAC help establish the diagnosis of a patient with a cystic mass of the neck. Titchener and Allison were able to establish a correct preoperative diagnosis in only 2 out of 4 cases, and have

emphasized the role of preoperative ultrasonography of the neck and FNAC to assess such cases.⁶ These lesions can be easily assessed using sonography because of their typically superficial nature.⁷ USG and FNAC are particularly advocated for patients in the older age group to rule out cystic secondaries from head and neck malignancies.

However, even the advanced diagnostic tools may fail to rule out the presence of malignancy within a cystic mass in the neck. Hence, cyst biopsy is required to exclude malignancy, especially in patients above 40 years of age. Frozen section at the time of cyst excision may be performed. Surgical excision of these lesions is reasoned curative and recurrence is unlikely if all remnants are excised.¹

Lateral cervical cysts containing squamous cell carcinoma may represent a cystic metastasis from an occult carcinoma. Several imaging techniques or even blind biopsies can detect the primary tumor. If the primary tumor is detected, an appropriate decision regarding treatment can be made encompassing both the primary tumor and the cervical node. However, if the primary tumor is not identified, treatment involves a modified or radical neck dissection, based on the extent of metastatic disease, and radiation therapy should be administered to Waldeyer's ring and both sides of the neck.⁸

CONCLUSION

The case presented here reinstates the utility of ultrasonography of the neck and FNAC in establishing

the diagnosis of lateral cervical cyst. Excision is the treatment of choice.

In our patient, we excised the cyst completely and the patient has been doing well since 3 months post-surgery.

Acknowledgment

Authors are grateful to Dr VK Mahadik, Medical Director, RD Gardi Medical College and Ujjain Charitable Trust Hospital, Ujjain (MP), for giving permission to publish this paper and for encouragement and support.

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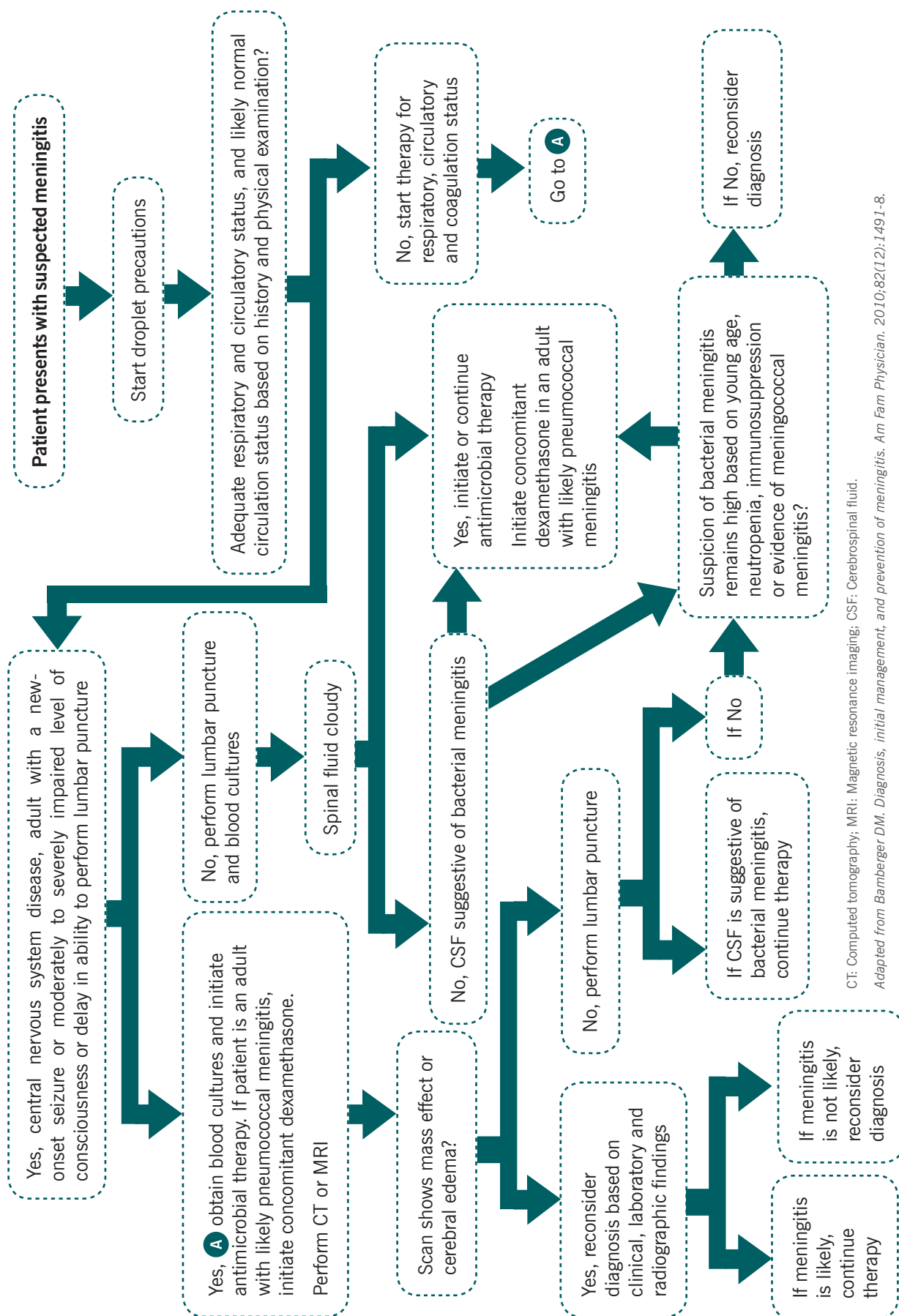
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Right to Avail Health Insurance is an Integral Part of the Right to Healthcare and the Right to Health, as Recognised in Article 21 of the Constitution of India, 1950

The Hon'ble High Court of Delhi in the matter titled as **M/ s. United India Insurance Company Limited versus Jai Parkash Tayal, RFA No.**

has considered the issue of whether persons having genetic disorders can be discriminated against in the context of health insurance.

FACTS OF THE CASE

Mr Jai Prakash Tayal, who is the Respondent/Plaintiff in the case (*hereinafter referred to as "Plaintiff"*), took an insurance policy for himself along with his wife and daughter, from the United India Insurance Company Limited i.e., the Appellant/Defendant in the case (*hereinafter referred to as "Defendant"*). The said policy is a mediclaim policy where the sum insured is Rs. 5 lakhs per individual. The Plaintiff submits he had first taken a mediclaim on 11th September, 2000 with the National Insurance Co. Ltd. vide policy No. 2000/8100540. The said policy was shifted to Defendant on 10th September, 2004, after which the policy was renewed continuously year to year without break till 10th September, 2012. The Plaintiff suffered from HOCM i.e., Hypertrophic Obstructive Cardiomyopathy (*hereinafter referred to as "HOCM"*). He was hospitalised on 23rd January, 2004 and 27th February, 2006 and his claims for the said periods have been honoured and payments were made by the Insurance Company.

Thereafter, the Plaintiff was again hospitalised for treatment on 27th November, 2011 and was discharged on 30th November, 2011. He made a claim for an amount of ₹ 7,78,864/- with the Defendant. The said claim was rejected vide letter dated 6th February, 2012, where the reasons for rejection were mentioned as—

"...We are closing your claim file, on account of the following reasons: TPA Vipun Medcorp P Ltd had repudiated your claim. Since genetic diseases are not payable as per the policy, genetic exclusion clauses." (extracted verbatim)

It is the Plaintiff's case that the exclusion of genetic disorders was not a part of the initial policy which was availed by him but was added as part of the 'Exclusions' in a later policy document, without specific notice to him and hence the said exclusions do not bind him. However, the stand of the Defendant was that HOCM is a genetic disorder which is clearly excluded and hence the claim is not liable to be entertained.

Thereafter the Plaintiff issued a legal notice to the Defendant, which was duly replied by the defendant whereby the Defendant refused to pay the claim as the genetic disorders are excluded in the policy document.

Thereafter, the Plaintiff filed a civil suit for recovery of an amount of ₹ 7,78,864/- against the Defendant. In the said civil suit for recovery, the Learned Trial Court vide judgement held that an insurance policy has to be renewed on the existing terms and conditions, and at the time of renewal, fresh clauses and exclusions cannot be added. The Learned Trial Court held that no advance notice was given to the Plaintiff and that some new clauses have been added to the policy.

The Learned Trial Court thereafter went into the question of whether the ailment of the Plaintiff was validly excluded from the mediclaim policy, and if so, had the Defendant acted contrary to law. The Learned Trial Court observed that twice in the past, for the same disease, the claims of the Plaintiff had been approved. The Learned Trial Court thereafter held that there cannot be a discriminatory clause against those persons who suffered from genetic disorders and they are entitled to medical insurance. The Learned Trial Court decreed the suit for a sum of ₹ 5 Lakhs along with interest of 8% per annum and rejected the claim for damages of ₹ 2,78,864/-.

Being aggrieved by the decree and judgement of the Learned Trial Court, the Defendant ie, United Insurance India Company Limited filed an appeal before the Hon'ble High Court of Delhi.

The two clauses from the insurance policy which are relevant to the case at hand are—

"1.1 NOW THIS POLICY WITNESSES that subject to the terms, conditions, exclusions and definitions contained herein or endorsed, or otherwise expressed here on the Company undertakes that during the period stated in the Schedule, if any insured person(s) contracts any disease or suffers from any illness (hereinafter called INJURY) and is such disease or injury requires such insured Person upon the advice of a duly qualified Physician/Medical Specialist/Medical Practitioner (hereinafter called MEDICAL PRACTITIONER) or of a duly qualified Surgeon (hereinafter called SURGEON) to incur hospitalisation/domiciliary hospitalisation expenses or medical/surgical treatment at any Nursing Home/Hospital in India as herein defined (hereinafter called HOSPITAL) as an inpatient, the Company will pay through TPA to the Hospital/Nursing Home or the Insured Person the amount of such expenses as are reasonably and necessarily incurred in respect thereof by or on behalf of such Insured Person but not exceeding the Sum Insured in aggregate in any one period of insurance stated in the schedule hereto

4 EXCLUSIONS:- . 4 4

1 Genetic disorders and stem cell implantation/ Surgery" Thus, the Insurance Company would pay the sum insured in the policy § subject to" the exclusion clause. If the medical condition is covered by any of the exclusions, the claim is liable to be disallowed. ¶ "Genetic disorders" is one such exclusion.

The Hon'ble High Court of Delhi considered two questions in the present appeal which are as follows—

- (i) Whether the exclusion in relation to ¶ "Genetic disorders" is valid and legal?
- (ii) Whether the exclusionary clause 1 relied upon by the Defendant for rejecting the claim of the Plaintiff applies on facts?

Judgement of Hon'ble High Court of Delhi

After hearing the submissions and taking into consideration the laws and norms in the foreign jurisdictions and the Indian Position, the Hon'ble High Court of Delhi held that

F T o conclude:

- (i) *Right to avail health insurance is an integral part of the Right to Healthcare and the Right to Health, as recognised in Art. 21 of the Constitution;*
- (ii) *Discrimination in health insurance against individuals based on their genetic disposition or genetic heritage, in the absence of appropriate genetic testing and laying down of intelligible differentia, is Unconstitutional;*
- (iii) *The broad exclusion of "genetic disorders" is thus not merely a contractual issue between the insurance company and the insured but spills into the broader canvas of Right to Health. There appears to be an urgent need to frame a proper framework to prevent against genetic discrimination as also to protect collection, preservation and confidentiality of genetic data. Insurance companies are free to structure their contracts based on reasonable and intelligible factors which should not be arbitrary and in any case cannot be "exclusionary". Such contracts have to be based on empirical testing and data and cannot be simply on the basis of subjective or vague factors. It is for lawmakers to take the necessary steps in this regard.*
- (iv) *The Exclusionary clause of "genetic disorders", in the insurance policy, is too broad, ambiguous and discriminatory - hence violative of Art. 14 of the Constitution of India;*
- (v) *Insurance Regulatory Development Authority of India (IRDA) is directed to re-look at the Exclusionary clauses in insurance contracts and ensure that insurance companies do not reject claims on the basis of exclusions relating to genetic disorders.*

Thus, the Hon'ble High Court upheld the judgement of the Learned Trial Court and held that:

"F.2. The Trial Court has rightly held that a person, suffering from a genetic disorder, needs medical insurance as much as others. The suit is decreed for a sum of Rs. 5 lakhs along with interest @12% from the date of filing of the claim with the Appellant Insurance Company till the date of payment;

F.3. The Plaintiff has been contesting the appeal for more than one and a half years and though the money has been released to him, he has submitted a bank guarantee to secure the said amount. The suit was filed in the year 2012. The Plaintiff is entitled to costs. Costs of ₹ 50,000/- are awarded. The bank guarantee submitted by the Plaintiff is released. All pending CMs are disposed of."

■ ■ ■ ■

HCFI Dr KK Aggarwal Research Fund

Minutes of Virtual Meeting of CMAAO NMAs on “Role of Baricitinib - JAK Inhibitor in Moderate-to- Severe COVID-19 and Country Updates”

5 h June, 12 (Saturday, 9 am-10 am)

Key points from the discussion

#1. JAK Inhibitor in moderate-to-severe COVID-19

Dr Rohit Aggarwal, Medical Director, Arthritis and Autoimmunity Center, Professor of Medicine, University of Pittsburgh

- In patients with severe coronavirus disease 2019 (COVID-19), the cytokine storm can cause significant lung damage; it can also damage other organs including the brain, kidneys and blood vessels via endothelial disruption and angiogenesis.
- The plasma levels of the proinflammatory cytokine interleukin (IL)-6 are raised; it is a prognostic indicator of mortality. It acts mainly through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which can be blocked by JAK inhibitors.
- All JAK inhibitors block different types of JAK receptors - JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk 2). Different JAK inhibitors block different types of cytokines; the advantage of using JAK inhibitors is that they block multiple cytokines.
- Baricitinib is a JAK inhibitor. It has a dual mode of action. By inhibiting numb-associated kinases (NAKs) and thereby viral endocytosis, it reduces viral infectivity. It exerts anti-inflammatory action via blockade of JAK1/2. IL-6 and interferon (IFN) are the cytokines where baricitinib is really believed to work.
- Baricitinib is an oral drug, so easy to administer; 4 mg once daily × 7-14 days or until discharge. Recommended for use only in hospitalized COVID patients requiring oxygen and high CAP.
- In an observational study from Italy, baricitinib arm vs. nonbaricitinib arm; Patients also got hydroxychloroquine (HCQ), lopinavir/ritonavir, antibiotics, steroids and low-molecular-weight heparin (LMWH) - Death or invasive mechanical ventilation was almost 7% in baricitinib group. It was almost double in the comparator group.
- Baricitinib was also independently associated as a protective variable with the primary outcome of death/ventilation in multivariate cox regression analysis. Very importantly, the favorable effect of baricitinib was seen early and persisted until the end of follow-up. In this study, there were some cases of liver enzyme elevation, but they did not require discontinuation of drug. Other side effects were lymphocytopenia, infectious complications. There were no signs of coagulopathy or thrombosis; but most patients were anticoagulated with LMWH.
- Baricitinib + remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19 especially among those receiving high-flow oxygen or noninvasive ventilation (NEJM, March 11).
- Results from the Phase 3 COV-BARRIER study of baricitinib 4 mg once daily + standard of care vs. placebo + SoC show that it did not meet the primary endpoint (patients progressing to the first occurrence of noninvasive ventilation including high-flow oxygen or invasive mechanical ventilation including extracorporeal membrane oxygenation [ECMO] or death by Day 28). A significant reduction in death from any cause by 8% was noted.
- The US Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) to permit the emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation or ECMO.
- Immune profiling with vaccine is very different from that with native infection.
- COVID vaccine can generate aberrant immune responses leading to autoimmunity, especially in patients who are more predisposed, but they are rare. Post-vaccine lupus-like syndrome has been reported.
- Tocilizumab vis-a-vis baricitinib: Tocilizumab is a specific IFN inhibitor; it inhibits IL-6, while baricitinib inhibits multiple cytokines; therefore using baricitinib might be better if one is

not sure that the inflammation is IL-6 driven. But, it has to be decided on case-to-case. Tocilizumab is to be given in hospital-setting as is baricitinib.

- We do not know yet if the vaccine-induced complications are reversible or permanent. We are still learning in the short-term.
- Repeat a negative antibody test after a vaccine/infection. Immune suppression drugs reduce vaccine response.

#2. Country Updates

- **India Update:** The second wave is receding. At the peak, there were more than 4 lakh cases; the number has declined to less 1.2 lakhs (at the time of meeting). Vaccination is ongoing on a large scale and more than 17 crore people have been vaccinated (at the time of meeting). There are chances of reinfection with the delta variant (B.1.617.2) even after full vaccination. The infectivity is higher, but duration of infection has reduced (≤ 1 week); also, mortality has not increased. Children are also getting infected; the Federation of Obstetricians and Gynaecologists Society of India (FOGSI) is now recommending vaccination for pregnant women.
- **Bangladesh Update:** Cases are high in areas bordering India; the delta variant is predominant strain now.
About 100 new cases per day and 10 deaths per day now (at the time of meeting).
- **Hong Kong Update:** There had been zero cases since more than a month; but yesterday, there has been a confirmed case of a 17-year-old student who did not travel anywhere or had a history of close contact with any confirmed cases. This is a case of unknown origin, which is alarming. Another cause of worry is the case of a medical student, who developed intracerebral hemorrhage after the vaccination. The government will now provide 1 day off after the vaccination for civil servants.
- **Pakistan Update:** The third wave has reached its peak; the positivity rate has come down from 2% to 2%. Earlier the UK variant was the major strain, but now 3 cases of variant from India have been detected, which is worrying.
- **Malaysia Update:** The country is in the fourth phase of the infection. Cases are increasing; there are around 7,000-8,000 cases per day, deaths are now 90-100 per day (at the time of meeting). There is a total lockdown during which only 20% of the workforce

will work. The government is trying to rope in the private sector to help them with the vaccination. The vaccination process is very slow. Doctors have died from the infection even after full vaccination.

- **South Africa Update:** The country is in the midst of the third wave; numbers are rising. It's the flu season in South Africa; it's difficult to differentiate between COVID and mild flu and colds. South Africa did not use AstraZeneca vaccine as it was shown to be not effective against the South Africa variant, which is causing the bulk of cases in the country. Hence, J&J and Pfizer vaccines are now used. Pfizer vaccine has been started only recently. The gap between first second doses has been expanded from 2 to 4 days.
- **Nepal Update:** There is a second wave in the country; about 100 new infections occur per day and around 10 deaths per day; deaths have reduced to around 10 per day. All healthcare workers (HCWs) have been vaccinated; the general population is hesitant to take the vaccine. There is scarcity of oxygen, beds and ICUs, etc. The country is in a strict lockdown. Death rate is very high in patients on ventilators with a recovery rate of less than 1%.
- **Australia Update:** About 45 cases of the delta variant, in a family who had traveled to NSW, have been detected. This is worrying and authorities are trying to trace the source of infection. The lockdown may get extended on account of these cases. Vaccination is slow.
- **Singapore Update:** The serial interval is very short, about 2-3 days indicating high transmissibility. There were 7 cases yesterday. Of these, one is an unlinked case. Four million of the total population of 5.5 million has been vaccinated (at the time of meeting). About 2.2 million have received the first dose; the rest have received both doses. Children are now being vaccinated.

Participants - Member NMAs: Dr YehWoei Chong, Singapore Medical Association, Chair CMAAO; Dr Ravi Naidu, Malaysian Medical Association, Immediate Past President-CMAAO; Prof Ashraf Nizami, First Vice President-CMAAO, President-PMA Lahore; Dr Alvin Yee-Shing Chan, Hong Kong Medical Association, Treasurer-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Salma Kundi, President, Pakistan Medical Association; Dr Angelique Coetzee, President-South African Medical Association; Dr Marie Uzawa Urabe, Japan Medical Association; Dr Md Jamaluddin Chowdhury, Bangladesh Medical Association; Dr Akhtar

Hussain, South African Medical Association; Dr Mukti Shrestha, Nepal Medical Association

Invitees: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr Brahm Vasudev, USA; Dr Monica Vasudev, USA; Dr Rohit Aggarwal, USA; Dr Sumit Soni; Dr Rishabh Popli; Dr S Sharma, Editor-IJCP Group; Dr Meenakshi Bamalwa Soni, HCFI

Moderator: Mr Saurabh Aggarwal

Minutes of Virtual Meeting of CMAAO NMAs on "Impact of COVID-19 on Mental Health of Healthcare Workers"

1 h June, 02 (Saturday, 09 am-01 am)

Key points from the discussion

- A presentation on "COVID-19 and mental health of healthcare workers" was given by Dr Avinash Hosanagar, Assistant Professor, Michigan Medicine and Staff Psychiatrist, Ann Arbor VA.
- Several studies have shown high prevalence of mental health problems in HCWs such as distress, depression, anxiety, insomnia; also, HCWs who feared infection of their close ones experienced high levels of stress, anxiety and depression. About one-third of HCWs experienced burnout syndrome (emotional exhaustion, sense of low personal achievement).
- Anxiety disorder and depression was highest among frontline HCWs and more so in those with clinical responsibilities. Nurses and female HCWs had more moderate-to-severe somatic symptoms.
- Gender and occupational differences were observed in a systematic review and meta-analysis with female healthcare professionals (HCPs) and nurses showing higher rates of mood and anxiety symptoms than the male HCWs.
- When the cases are going up in the early phase, there is fear for basic needs, especially among the HCWs. As the situation plateaus, there is uncertainty of how things will evolve and when the situation shows a decline, we feel better but there is a need for processing of all traumatic experiences that people have undergone.
- People go through emotional highs and lows. During the initial period, there is lot of heroism and people come together (resilience). As the pandemic continues, a period of disillusionment sets in; emotional lows occur during this period. This is followed by a very gradual period of restoration, where people work through their grief and adjust to their new lifestyle and situation and rebuild. People experience negative emotions during the disillusionment period, lot of trigger events and anniversary reactions happen leading to psychological trauma manifesting as anxiety and depression.
- During a pandemic (disaster), people may have distress reactions in the form of sleep difficulties, decreased sense of safety, irritability, anger, distraction and isolation. They may also engage in risky behaviors such as alcohol, tobacco to cope with the stress. There may be family distress, interpersonal conflict/violence, disrupted work-life balance especially in the context of restricted activities.
- The challenges faced by HCWs are unprecedented during these COVID times such as a high demand for medical services over a long period of time, HCWs have been forced to step up into roles outside of their areas of expertise, COVID-19 management protocols are uncertain and still evolving, fear of contracting the infection and spreading it to family members and coworkers. HCWs who get infected or experience burn out due to the high volume of the work may result in absenteeism and staff shortage.
- A survey of HCWs undertaken to identify their sources of anxiety revealed the following sources: Access to the right personal protective equipment (PPE); exposure to COVID at work and taking the infection home to their families; lack of fast access to testing if symptoms develop and fear of spreading the infection at workplace and uncertainty whether their organization will support and take care of their personal and family needs if they develop infection; support for transportation, food and family needs as work hours and demands increase; access to childcare when working extra hours and schools are closed; having the right skills if sent to work in a new area and lack of access to up-to-date information and communication.
- The American Psychological Association (APA) experts committee has suggested that it is important to recognize that exposure to death (especially in high volumes) with ongoing risk for HCW for families is an extreme stressor. HCWs face challenges of workers with less experience of intensive care settings like ICUs, inadequate evidence base for treatment, insufficient resources including lack of optimal self-protection, obstacles to meaningful connection with patients and diminished access to HCWs support system such as families.

- Principles of psychological first aid have been advised, which include promoting a sense of safety as much as possible, helping them use self-calming techniques, promoting basic self-care during the pandemic, encourage use of prior helpful coping mechanisms, access to stress reduction resources, create a sense of team, promote social support, monitor those in high distress and get appropriate additional mental health team support.
 - It is important to be mindful of individual differences in response to death. One must focus on what we can control and accept what we cannot.
 - Factors like the heavy workload, high death rates and inability to follow usual routines increase the stress. Talking about these can help the HCWs. Their efforts during these times should be regularly recognized and honored.
 - The leadership should actively respond to the needs and concerns of the HCWs, which include working without needed PPE or safeguards, witnessing human suffering, making life and death decisions, fear of infecting family members, separation from family, fear of getting sick and mental exhaustion.
 - How can leaders help? By leading them with model behaviors (e.g., wearing masks at all times so that the rest of the team can follow), listen to them, protect them, prepare them (to be proactive when numbers come down), support them and care for them.
 - Things that will help in this direction: Talk directly with your staff and listen, walk the floors weekly to show your support for workers, model the right way to put on and take off PPE, set up a buddy system, post or share tools and resources, give support to HCWs, communicate clearly, as often as possible and let teams know. Keeping them informed is critical. The more you talk to your team, the better prepared they will be to manage your patients.
 - A new phenomenon of moral distress leading to moral injury in HCWs and its implication in work life has been described in this pandemic. Moral injury is known in psychiatry as occurring in military persons and is now being identified in HCWs.
 - Moral injury is worsened when the healthcare system is overwhelmed when decisions have to be made about allocation of scarce medical resources to patients.
 - All HCWs experience moral injury but in different domains. Moral injury will lead to burnout and ultimately poor productivity.
 - A “post-traumatic embitterment disorder” (PTED) has also been recognized.
 - This moral distress would be carried over even beyond the pandemic as well.
 - Toxic stress is related to inflammatory processes and oxidative stress.
 - There are no studies that have examined the impact of burnout syndrome on families and rest of the society specifically in terms of the current COVID-19 pandemic, but there are enough studies on the impact of burnout on work and productivity in a hospital system.
 - Burnout results in smaller work force, people choosing other professions outside of medicine, less productivity in work on a day-to-day basis. All these affect the number of patients seen, the quality of care provided and the patient outcomes. Burnout has a huge economic impact.
 - We need to learn from this pandemic and prepare the next generation for this. We must take note of what happened including mistakes that happened. This pandemic has exposed the fragility of healthcare systems. It is our responsibility to get the healthcare system where it needs to be for future situations.
 - As leaders of NMAs, we have to make sure that we are heard. This is a time for advocating for healthcare resources that we need. We need to be more proactive.
- Participants - Member NMAs:** Dr Yeh Wei Chong, Singapore, Chair CMAAO; Dr Ravi Naidu, Malaysia, Immediate Past President-CMAAO; Prof Ashraf Nizami, Pakistan, First Vice President-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Salma Kundi, Pakistan; Dr Qaiser Sajjad, Pakistan; Dr Angelique Coetzee, South Africa; Dr Akhtar Hussain, South Africa; Dr Md Jamaluddin Chowdhury, Bangladesh
- Invitees:** Dr Russell D’Souza, Australia UNESCO Chair in Bioethics; Dr Shashank Joshi, Endocrinologist, Mumbai, India; Dr Monica Vasudev, Allergist-Immunologist, USA; Dr Nidhi Aggarwal, Pathologist, USA; Dr Muzammil Hussain Bukhari, Pakistan; Dr S Sharma, Editor-IJCP Group; Dr Meenakshi Bamelwa Soni, HCFI
- Moderator:** Mr Saurabh Aggarwal

72nd Annual Cardiology Conference

STATIN FOR PRIMARY PREVENTION: WHOM AND WHEN?

Prof (Dr) Saumitra Ray, Kolkata

Statins are among the most successful therapies known to reduce cardiovascular (CV) risk and are rightfully commonplace in the personalized treatment of asymptomatic adults with coronary risk factors or known atherosclerotic vascular disease. Prescribing a generic statin to a middle-aged or older adult with hyperlipidemia and another risk factor is viewed by Preventive Cardiologists as one of the certainties of life.

Statin: When Lifestyle Changes are not Enough

Statin treatment is not a replacement for lifestyle changes, but the two are often key components of a multifactorial approach to CV risk reduction. When cardiovascular risk factors develop and therapeutic lifestyle changes are insufficient, then it is time to talk about the potential beneficial role of statin therapy to change the natural history of the atherosclerotic disease process. Deciding whether adults with an elevated risk of a subsequent cardiovascular disease (CVD) event over the next decade might benefit from a generic statin requires an honest analysis of whether the potential benefits outweigh the possible risks. Therefore, a brief review of statin benefits and risks is warranted.

"Normal" Cholesterol: Loosening the Belt

From an evolutionary standpoint, humans were not intended to have lipid levels in the ranges currently considered normal. According to the National Cholesterol Education Program, Adult Treatment Panel (NCEP-ATP), low-density lipoprotein cholesterol (LDL-C) levels 100-129 mg/dL are "near-optimal" and levels 130-159 mg/dL are "borderline high." In our lipid-laden, overweight, sedentary culture, atherosclerosis abounds, starting early in life.

Is Statin Right for Your Primary Prevention Patient?

A statin should be used in primary prevention when the benefits outweigh the risks. Therefore, the decision should be based on risk assessment. Given that statins have a very low risk of major side effects, for many patients, the risk-benefit equation will be in favor of therapy.

Selective use of statins in the primary prevention setting is simply a matter of doing the right thing in the right

patient at the right time based on the convincing totality of the evidence.

Suggested Reading: ¹Who Should Get Statins for Primary Prevention, Seth Shay Martin, MD, MHS, FACC; Aaron Horne, Jr., MD; Roger S. Blumenthal, MD, FACC. ²Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97. ³Grundey SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol. 2004;44:720-32.

BENEFITS OF EXERCISE ARE DIFFERENT WITH GENDER

Dr Rachel Daniel, Kollam

Men and women report different exercise habits and reasons for exercise. Women reported exercising for weight loss and toning more than men, whereas men reported exercising for enjoyment more than women. Females' requirements for exercise might well differ from that of males. Males gain health benefits from vigorous physical activity (6 METs) while females from low (3 METs) to moderate (3-6 METs) intensities. There is a relative contribution of "nature versus nurture" in the observed difference in physical activity levels and exercise behavior between males and females. The gender difference in exercise is due to difference in: 1) body composition; 2) CV difference and maximal oxygen uptake; 3) muscle fiber type composition; 4) anaerobic and aerobic exercise capacity; 5) fuel resources during exercise. There are clear limitations to a "one size fits all" approach for recommending doses of exercise or physical activity to achieve health benefits at the population level. Males and females are predisposed to engage in different levels of intensity and type of physical activity, which should be reflected in policy and practice.

RISKS OF CVD IN MEAT EATERS, FISH EATERS AND VEGETARIANS – YOUR RISK IS WHAT YOU EAT!

Dr Amit Malviya, Shillong

No randomized controlled studies are available to differentiate the cardiac outcomes of vegetarian versus

nonvegetarian diets. The EPIC-OXFORD study has shown a lower risk in vegetarians and vegans that remained marginally significant after adjustment for all of these factors. The reasons for such differences are not certain but could be partly attributed to lower concentrations of LDL-C (LDL-C, or non-HDL-C [high-density lipoprotein cholesterol] concentrations as a surrogate) associated with meat-free diets. In the EAT-Lancet commission on healthy diets from the sustainable food system report defined a universal reference diet to promote human and environmental health. It showed that high adherence to the EAT-Lancet score was linked with lower risks of ischemic heart disease (28%) and diabetes (9%).

SFA TOTAL OCCLUSION IN CRITICAL LIMB ISCHEMIA – STENTING WILL BE MY BAILOUT OPTION

Dr James Thomas, Kottayam

In critical limb ischemia (CLI), femoropopliteal stenosis/total occlusions are classified based on their length. Focal lesions (≤ 10 mm) can very well be treated with plain balloon dilatation itself. Even the favorable data for stenting in long lesions has been derived from studies in which percentage of CLI patients was very low. The endpoints of most of these studies were Doppler restenosis and claudication distances, etc, and not those parameters pertinent to CLI (eg, limb salvage, amputation free survival, major adverse limb events, etc). So, the data favoring femoropopliteal stenting cannot be extrapolated to CLI subgroup. Stenting in femoropopliteal segment has many issues, like stent fracture. Restenosis after stenting also makes further revascularization options very limited. The current concept of 'Leave nothing behind' is promising, and uses drug-eluting balloons (DEBs) as final therapy, avoiding stents (though controversial, because of excess mortality seen with femoropopliteal DEB therapy in some studies). Drug-eluting stents are not yet available in India, even though have shown promising data. Putting it all together, it can be concluded that stenting should be used only as a bailout option in femoropopliteal angioplasty in CLI.

EARLY DETECTION AND TREATMENT OF THE VULNERABLE CORONARY PLAQUE – CAN WE PREVENT ACUTE CORONARY SYNDROMES?

Dr Monotosh Panja, Kolkata

- Invasive and noninvasive modalities: For early and accurate identification and prognostic value of vulnerable plaque.

- Noninvasive modalities: Critical for detection and treatment of vulnerable plaque for large and low-risk populations.
- Statin therapy-induced plaque stabilization to reduce CV events-acute coronary syndrome (ACS). Intensive statin therapy has demonstrated a significant reduction in coronary events in patients of stable angina (TNT and IDEAL trials) and ACS (PROVE-IT TIMI trial). ASTEROID trial has shown an absolute reduction in atheroma volume with rosuvastatin.
- Anti-inflammatory drugs are needed to reduce CV outcome - Personalized treatment of CVD is both inevitable and indispensable.

LONG-TERM ANTITHROMBOTIC THERAPY IN HIGH-RISK PCI – CONSIDER LOW-DOSE RIVAROXABAN WITH SAPT

Dr M Srinivasa Rao, Hyderabad

Patients with known coronary artery disease (CAD) remain at risk of recurrent events despite revascularization with the percutaneous coronary intervention (PCI). The mechanism may be related to impaired healing and delayed re-endothelialization after stent placement, triggering platelet activation and thrombus formation. Accelerated neoatherosclerosis can lead to subsequent atherothrombotic events. However, frequently occurring events are remote from the stent implantation site, the pathophysiology of which is related to rupture or erosion of atherosclerotic plaque. In a chronic coronary syndrome population, there is limited contemporary information assessing the long-term outcomes and impact of various antithrombotic strategies of those with or without previous PCI. The landmark COMPASS-PCI study found that the combination of low-dose rivaroxaban and aspirin in comparison with aspirin alone reduced the primary composite of CV death, myocardial infarction or stroke, as well as all-cause death (and cardiovascular mortality), with or without previous PCI in chronic coronary syndromes.

In patients with the previous PCI, consistent (robust) reductions in the primary endpoint and all-cause mortality were demonstrated with low-dose rivaroxaban and aspirin irrespective of the timing of the previous PCI as early as 1 year and as far back as 10 years. These findings support the addition of low-dose rivaroxaban (2 mg twice daily) to low-dose aspirin in high-risk patients with a chronic coronary syndrome with a history of PCI (at least 1 year), irrespective of the timing of the previous PCI (as far back as 10 years), who are not at high bleeding risk.

CARDIOVASCULAR DISEASE: MY JOURNEY FOR THE SEARCH OF FONS ET ORIGO OR ROOTS

Dr MK Das, Kolkata

- In quest of behavior of conduction tissue at different locations, we conducted a study with 2 patients and noted that 8% cases of sinus node dysfunction (SND) diagnosed by clinical, ECG or EP criteria had atrioventricular nodal block or infranodal block. For the first time, we demonstrated convincing EP evidence of sinus node dysfunction in such conditions and termed the same as Pan-Conduction System Disease or Das and Barooah syndrome.
- Atrial fibrillation (AF) and pacing – Single operator retrospective observational data from a cohort of 8 patients who underwent PPI between 2 and 8 in 3 hospitals at Kolkata: It was found that SND has more propensity to develop AF; Single chamber pacing has more propensity to develop AF.
- Pan-Conduction System Disease with combination of SND and AV or infranodal disease with symptoms is to be considered before embarking on the pacing therapy.
- Direct oral anticoagulants (DOACs) or non-vitamin K oral anticoagulants (NOACs) are quite useful, effective and safe for AF and prevent stroke/TE (thromboembolism).
- Risk factors and angiographic profile of CAD in young – Number of vessels affected appears to be directly proportional to the number of risk factors associated. Modifiable risk factors include behavioral (tobacco, diet, physical inactivity, stress) and biological (high BP, diabetes, dyslipidemia, central obesity); they influence the development of the disease. A study in school-going children revealed that obesity and hypertension are real problems. Despite knowing so much about ambulatory BP monitoring, home BP monitoring, white coat hypertension, masked hypertension, BP variability, etc, why are things still not under control?
- Total value of BP surge differentials becomes a huge number, which can have a huge impact on the CV system. This has been proposed as a novel concept. Continuous high BP levels trigger genetic mechanisms and influence the blood vessels and target organs, thus causing target organ damage. Combination of drugs is being proposed to be used which is a rational approach to attack the multiple roots. Single polypill conundrum has to

be accepted as a rational approach. There is a role of digital technology and augmented intelligence in finding roots and also influencing treatment schedule. Digital therapeutics is an important step in the right direction. Translational or precision medicine is going to change our concepts in dealing with patients.

- Coronavirus disease 2 (COVID-19) has promoted leadership in a different way. A leader has to control the damage; lead from the front. A leader should have the quality to inspire the next generation.

STATIN IN ACS PATIENTS WITH CKD

Dr Gurunath Parale, Solapur

Data collected from a trial on 8 patients of the National Registry of MI suggest that administration of statins within 2 hours after hospitalization for AMI lower the rate of early complications and in hospital mortality. This beneficial effect is probably due to the pleiotropic effect of statins. Statins are known to dampen inflammation, ED and coagulation disorders observed after MI. Despite ample evidence, statins are less likely to be used for ACS in patients with chronic kidney disease (CKD). The reason for this reluctant use of statin is not clear. Concerns for further renal damage and other toxic side effects may be the probable explanation. In addition, since the patients with CKD are likely to harbor other comorbidities, contraindications for the use of statins may increase. Another probable reason for the reduced use of statins is that some uncertainty lingers regarding their therapeutics benefits in patients with kidney disease. No clear evidence is found in patients of CKD regarding a positive relationship between blood cholesterol and CV events. Since chronic malnutrition and inflammation are common in severe CKD, the blood cholesterol levels ultimately drop in CKD patients. This U-shaped relationship between dyslipidemia and CV events in patients with CKD and coronary heart disease (CHD) is often described as low cholesterol paradox. This paradox has raised suspicion regarding utility of lipid-lowering therapy. In addition, some concerns about drug toxicity due to high-dose statins persists in patients of CKD. Increased risk of myopathy is reported due to use of statin in patients with kidney dysfunction. However, a recent study of heart and renal protection trial has shown that combination of Ezetimibe and low-dose statins can safely reduce the risk of major atherosclerotic events in a wide range of patients with CKD including patients on dialysis.

News and Views

Pfizer to Test Its COVID-19 Vaccine in Larger Group of Children Below 12 Years

Pfizer Inc has said that it is going to test its coronavirus disease 2019 (COVID-19) vaccine in a larger group of children below 12 years of age after selecting a lower dose in an earlier stage of the trial.

The study is set to include around 4,500 children across over 90 clinical sites in the United States, Finland, Poland and Spain. On the basis of safety, tolerability and the immune response observed among 144 children in a phase I study of the vaccine, the company is gearing to evaluate a dose of 10 µg in children aged 5 to 11 years, and a dose of 3 µg in those aged 6 months to 5 years.

Pfizer expects data from the group of 5 to 11 years old in September and would possibly seek emergency use authorization (EUA) later in that month. Data from children aged 2 to 5 years could be obtained soon after that, stated a company spokesperson. Data from the age group of 6 months to 2 years is expected in October or November... (*Reuters*)

Pfizer, Moderna COVID-19 Vaccines Reduce Infection Risk by 91%: US CDC

Administration of two doses of the Pfizer-BioNTech and Moderna mRNA-based COVID-19 vaccines can diminish the risk of COVID infection by 91%, suggests a new study by the US Centers for Disease Control and Prevention (CDC).

It was reported that even a single dose of the mRNA vaccines can decrease the risk of infection by 81%. The estimates include both symptomatic and asymptomatic infections. Additionally, the study suggested that mRNA vaccination is beneficial for individuals who get COVID-19 even after being fully vaccinated (14 or more days after second dose) or partially vaccinated (14 or more days following first dose to 13 days following second dose)... (*ET Healthworld – IANS*)

Covaxin Effective Against COVID-19 Variants: Study

India's indigenous COVID-19 vaccine, Bharat Biotech's Covaxin, has been found to be effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, including the Delta variant which was first detected in India, in a study by the Indian Council of Medical Research (ICMR).

The investigation also noted that the vaccine was three times as effective in developing antibodies as a prior COVID-19 infection. Furthermore, the vaccine was reported to create 2.7 times less neutralizing titer against the Delta variant and threefold less neutralizing titer against the Beta variant of the coronavirus, which was first detected in South Africa. However, the vaccine was effective against both strains... (*HT*)

Obese is also a Risk Factor for Long COVID

Obesity is an established risk factor for severity of COVID-19 infection as well as mortality. Now, a new Cleveland Clinic study has suggested that patients with obesity are also at greater risk for post-acute sequelae of SARS-CoV-2 infection (PASC), commonly referred to as "long COVID-19".

The study published in the journal *Diabetes, Obesity and Metabolism* involved 2,839 COVID-19 positive patients from a clinical registry of all patients tested positive by reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection, within the Cleveland Clinic health system in a 5-month period from March 2020 to July 2020, with follow-up until January 2021. These patients had not needed intensive care for their illness and had survived the acute infection.

Three parameters were assessed, namely hospital admission, need for diagnostic medical tests and death occurring ≥30 days after the first confirmatory test. Patients were categorized into five groups based on their body mass index (BMI): 18.5-24.9 (normal), 25-29.9 (overweight), 30-34.9 (mild obesity), 35-39.9 (moderate obesity) and ≥40 (severe obesity).

- During the follow-up of 10 months, 44% of patients had to be hospitalized; 1% of patients died during this time.
- The risk of hospital admission was 28% higher in patients with moderate obesity and 30% higher in those with severe obesity vs. patients with normal BMI.
- The need for diagnostic tests for various medical problems post-infection was found to be 25% and 39% higher in patients with moderate and severe obesity, respectively.

- Compared to patients with normal BMI, those with BMI ≥ 35 were more likely to require diagnostic tests to evaluate for cardiac, pulmonary, vascular, renal, gastrointestinal and mental health problems.

Although more studies need to be done to confirm these findings, this study does show that obesity just does not have an effect on the severity of infection; it also increases the risk for long-term complications of COVID-19 as evident by the fact that up to 44% of the patients required hospital admission during the follow-up period after the initial infection.

(Source: *Obesity increases risk for long-COVID, study finds* - Medscape - Jun 08, 2021; *Cleveland Clinic News Release*, June 3, 2021)

COVID-19 More Likely to Spread Indoors via Maskless Interactions

According to a new study published in the *Journal of Internal Medicine*, speaking without masks in closed spaces is tied to the greatest risk of transmission of SARS-CoV-2 virus to others.

The study elaborates on how respiratory droplets of different sizes expelled while speaking cover a continuum of sizes and can carry varying amounts of the virus. The intermediate-sized droplets remain in the air for minutes and can travel over considerable distances through convective air currents.

Adriaan Bax, from the US National Institute of Diabetes and Digestive and Kidney Diseases, said that when water evaporates from the potentially virus-rich droplets emitted while speaking, they float in the air for minutes, putting people at risk... (ET Healthworld – IANS)

Early Monoclonal Antibody Use Tied to Reduction in Hospitalizations and Mortality in High-risk COVID-19 Outpatients

A study published in *Clinical Infectious Diseases* suggests that early use of monoclonal antibody (mAb) was linked with a reduction in hospital admissions and mortality among high-risk outpatients with COVID-19.

A retrospective review of medical records of patients referred to a COVID-19 clinic between November 1, 2020 and February 28, 2021 was conducted that included 617 high-risk patients. All high-risk outpatients were offered casirivimab/imdevimab or bamlanivimab within 5 days of diagnosis. Overall, 175 patients were administered mAb (83.4% received casirivimab/imdevimab, 16.6% received bamlanivimab). Patients who received mAb had lower odds of being hospitalized in comparison with those in the control group (1.7% vs. 24%) with an

odds ratio (OR) of 0.0466 after adjustment for risk score and local pandemic intensity. No COVID-19-related deaths were noted in the mAb group while there were 12 deaths (2.7%) in the control group... (DG Alerts)

Covishield Vaccine Tied to Slightly Higher Risk of Bleeding Disorders, Says Study

People administered the Oxford-AstraZeneca COVID-19 vaccine, known as Covishield in India, had a slightly higher risk of a bleeding disorder and other rare blood problems, noted researchers.

The study included 2.53 million adults in Scotland who were given their first doses of either the AstraZeneca vaccine or the Pfizer-BioNTech vaccine. Around 1.7 million doses were of the AstraZeneca vaccine. There appeared to be no increased risk of blood disorders with the Pfizer-BioNTech vaccine.

The AstraZeneca vaccine was associated with a slight increase in the risk of immune thrombocytopenic purpura (ITP). The estimated risk was 1.13 cases per 1,00,000 people receiving their first dose, up to 27 days following vaccination. The study was published in *Nature Medicine*... (ET Healthworld – NY Times)

Novavax Says Its COVID-19 Vaccine Exhibits Immune Response Against Beta Variant

According to Novavax Inc, its experimental vaccine against COVID-19 exhibited immune response and protection against the highly contagious variant of the coronavirus that was first detected in South Africa, in a new study.

NVX-CoV2373, Novavax's vaccine against COVID-19, is being tested in several trials and is yet to receive authorization for use in any country. Novavax stated that trials in mice and baboons noted that a different vaccine, which particularly targets the Beta variant, produced immune response and protection. The company expects to carry out further clinical testing of the vaccine in the fall.

Analysis of blood serum of 30 participants in a mid-stage trial who had been administered both doses of NVX-CoV2373 noted robust antibody responses against the original version of the virus and against the Alpha variant first found in the UK as well as the Beta variant... (Reuters)

Another Rare Blood Condition Added as Side Effect of AstraZeneca Vaccine

The drug regulator of Europe has detected another very rare blood condition as a side effect of AstraZeneca

COVID-19 vaccine and is evaluating the cases of heart inflammation after vaccination with all COVID-19 vaccines.

According to the European Medicines Agency's (EMA) safety committee, capillary leak syndrome (CLS) should be added as a new side effect to the labeling on AstraZeneca vaccine. The EMA stated that individuals who had sustained the condition earlier, where fluids leak from the smallest blood vessels resulting in swelling and a fall in blood pressure, should not be given the jab.

Earlier, the EMA had advised against administering a second dose of the AstraZeneca vaccine to those who had a clotting condition, called thrombosis with thrombocytopenia syndrome (TTS)... (ET Healthworld – Reuters)

Delta Variant 60% More Transmissible: UK

The Delta coronavirus variant appears to be 60% more transmissible in households compared to the variant that caused UK to go into a lockdown in January, said the British Government.

The Delta variant has led to a spike in cases in the UK. New research from Public Health England indicates that the Delta variant is tied to about 60% increased risk of household transmission, in comparison with the Alpha variant first identified in Kent, southeast England.

The public vaccination drive has been ramped up and the government indicated that the vaccination drive is diminishing the impact of the Delta variant, and urged the people to get both vaccine doses... (NDTV – AFP)

Researchers Identify Batch of New Coronaviruses in Bats in China

Researchers in China have identified a batch of new coronaviruses among bats, including one that appears to be genetically the second-closest so far to the COVID-19 virus. These discoveries in a small region of Yunnan province, southwestern China suggest that several coronaviruses exist in bats and many have the potential to spread to humans. Researchers obtained samples from small, forest-dwelling bats from May, 2019 through November, 2020 and tested urine and feces as well as swabs from the bats' mouths. Twenty-four novel coronavirus genomes were identified among different bat species, which included four SARS-CoV-2 like coronaviruses. One of these was very similar genetically to the SARS-CoV-2 virus - a sample called RpYN06 obtained from a horseshoe bat species. The findings are published in the journal *Cell*... (CNN)

COVID-19 Linked to Rise in Suspected Suicide Attempts by Girls

New data from the US CDC indicate that suspected suicide attempts rose significantly among teenage girls during the pandemic.

Among children and adolescents, 12 to 17 years of age, the average weekly emergency department (ED) visits for suspected suicide attempts were found to be 22.3% higher during summer of 2020 and 39.1% higher during winter of 2021, compared to the figures during the corresponding periods in 2019. Additionally, the spike was most marked among young girls. From February 21 to March 20 this year, the number of ED visits for suspected suicide attempts was about 51% higher among girls in the 12 to 17 years age group compared to during the same period in 2019. ED visits for suspected suicide attempts were about 4% higher among boys in the same age group, reported the agency... (Medscape)

Two Doses of COVID Vaccine Offer 77% Protection Against Hospitalization: CMC Vellore Study

Two doses of COVID-19 vaccine are highly protective against infection and hospitalization even among healthcare workers (HCWs) who have a high risk of infection, suggests a study conducted at CMC Vellore.

The study noted that vaccination provided high protection; however, it did not evaluate the proportion of cases caused by the Beta (B.1.1.7) and Delta (B.1.617.2) variants. The investigators could not individually study the efficacy of Covishield and Covaxin as only a few of the study participants received Covaxin. Overall, 8991 HCWs were vaccinated from January 21 to April 30, 2021, with around 8,400 of them receiving Covishield. Of the 7,080 HCWs who were given two doses, the vaccines offered 65% protection against infection, 77% protection against hospital admission, 92% protection against oxygen requirement and 94% protection against admission to the ICU. The study is published in the journal *May Clinic Proceedings*... (The Hindu)

High Seroconversion Rates after COVID Vaccination in Cancer Patients

A study published in *Cancer Cell* suggests that cancer patients who were vaccinated against COVID-19 attained high seroconversion rates.

The rate of seroconversion was found to be particularly high among patients who had solid tumors (98%). Patients with hematological malignancies had lower rates of seroconversion (85%), especially those who had undergone highly immunosuppressive therapies.

Patients with hematological malignancies were also reported to have significantly lower titer levels in comparison with patients with solid tumor and noncancer controls, reported researchers. Balazs Halmos of Montefiore Medical Center in New York City stated that the study suggests COVID-19 vaccines are safe and effective for most patients with cancer... (*Medpage Today*)

Celltrion Says Its Antibody COVID-19 Treatment Found Safe and Effective in Trial

South Korea's Celltrion Inc has stated that Phase 3 global clinical trials have shown positive results for its experimental antibody treatment for COVID-19, which was found to be safe and decreased the treatment period by around 5 days.

The trials included 1,315 participants in 13 countries, including South Korea, the United States, Spain and Romania, and have taken place since January. The treatment slowed severe symptoms in over 70% of patients, including the high-risk patients with underlying conditions. The treatment was also found to reduce the recovery period by 4.9 days. South Korea had given conditional approval to the antibody treatment in the month of February, making it the first locally developed COVID-19 treatment in the country to receive such approval... (*Reuters*)

No Higher Risk to Children from Third COVID Wave, Says Report

A report from *The Lancet* COVID-19 Commission India Task Force has suggested that there appears to be no evidence to indicate that children have a higher risk of infection or are at greater danger from a COVID-19 infection from an expected third wave.

The group of experts was asked to evaluate the available evidence and recommend practical tools and strategies for providers, and guidance for policymakers and the public for addressing the disease in children. The evidence available thus far indicates that while children have milder disease, better prognosis and low mortality when compared to adults, those with underlying illness could have a higher risk... (*The Hindu*)

Impact of Discontinuing Antihypertensive Medications on Outcome of Hospitalized COVID-19 Patients

A study published in the journal *Hypertension* suggests that discontinuation of at-home angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers

(ARBs) or β -blockers (BB) in patients hospitalized for COVID-19 infection was tied to an increased risk of mortality, while discontinuation of calcium channel blockers (CCBs) and diuretics was not associated with a greater mortality risk.

Overall, 1,584 patients were included in the retrospective cohort study. Around 57.70% of the patients reported use of antihypertensive medications at home - 26.37% were using ARBs, 33.81% were on ACE inhibitor therapy, 57.33% were taking BB, 33.37% were on CCBs and 47.81% were taking diuretics. Of the total 914 patients who were on at-home antihypertensive medication, 270 discontinued it during hospitalization. Investigators noted that after adjusting for confounders including age, sex and modified early warning score at admission, discontinuation of ARBs (OR 2.65, 95% confidence interval [CI] 1.17-6.04, $p < 0.05$), ACE inhibitors (OR 2.28, 95% CI 1.15-4.54, $p < 0.05$) and BB (OR 3.60, 95% CI 1.10-10.27, $p < 0.05$) was linked with a heightened risk of death from COVID-19 infection. However, discontinuation of CCBs or diuretics was not tied to an increased mortality risk... (*DG Alerts*)

Increasing e-waste Affects Health of Children Across the Globe, Cautions WHO

The informal processing of scrapped electrical or electronic devices is putting the health of millions of children, adolescents and expectant mothers across the globe at risk, suggests a report from the WHO, titled *Children and Digital Dumpsites*, and calls for effective and urgent action to protect them.

Around 12.9 million women are working in the informal waste sector, and are exposed to toxic e-waste, which puts them and their unborn children at risk. Additionally, over 18 million children and adolescents, including some who are as young as 5 years old, are also involved in the informal industrial sector. Waste processing is a part of the sector. Furthermore, there are children who live, attend school and play near e-waste recycling centers, where toxic chemicals, especially lead and mercury, can potentially damage their intellectual abilities.

The report urges conclusive action by exporters, importers and governments to make sure that there is environmentally sound disposal of e-waste and to ensure the health and safety of workers and their families as well as communities at large. It also calls for monitoring of e-waste exposure and health outcomes, promoting better reuse of materials and encouraging the manufacture of more durable devices... (*WHO*)

■ ■ ■ ■

Am I a Spiritual Seeker?

Every one cannot be a spiritual seeker. A vast majority is not even interested in seeking spiritual knowledge and keep themselves busy in the worldly desires. To become a good seeker, one needs to acquire many qualities.

In *Bhagavad Gita*, Arjuna, in a state of disturbed mind, seeks guidance from Lord Krishna. In *Katha Upanishad*, Nachiketa, a healthy seeker, learned the knowledge of life after death from Yama. *Katha Upanishad* described in detail the qualities of a seeker in Nachiketa.

The story is as follows: Sage Vajashrava performed a sacrifice where he had to give away all his worldly possessions. His son Nachiketa saw that the cows given in the donations were old. He felt that such charity will not give his father any merits. Nachiketa asked his father to whom was he given. The sage ignored him twice, but when he asked for the third time, the irritated sage said, "Unto Yama, I give thee." Nachiketa went to the abode of Yama, and did not find him there. He waited there for 3 days and nights. When Yama returned, he offered to grant him three wishes.

Nachiketa wished the following:

- To return to his father alive, and that his father not be angry with him

- To be told about fire sacrifice
- To attain knowledge about life after death.

Yama granted the first wish immediately. For his second wish, Yama named performance of a special fire sacrifice after Nachiketa. Before granting the third wish, Yama tested Nachiketa. He offered him all sorts of worldly pleasures instead, but Nachiketa insisted on gaining the knowledge. Yama finally taught him about life after death.

The properties of true seeker, therefore, include:

- Righteousness and truthfulness: Nachiketa did not agree with his father as his father's act was not based on Dharma.
- Persistence: He waited for 3 days to meet Yama.
- Compassion and forgiveness: The first boon he asked was to have his father forgive him.
- Intellectual understanding: The fire of knowledge means intellectual understanding.
- Let go of the desires: He let go all his desires and did not get attracted to the worldly pleasures.

Only after all this, he could receive the knowledge of soul and become a true seeker.



Over 1 in 10 People have Missed their Second Dose of COVID-19 Vaccine in US

An increasing number of people, over 1 in 10 have missed their second dose of a COVID-19 vaccine in the US, which is a concern as the Delta variant is gaining pace. As of June 16 around 8% of those who received one dose of a COVID-19 vaccine and were eligible to receive their second dose, had completed their two dose series, revealed data obtained from the US CDC. This has decreased from a 9% completion rate observed earlier this year. Experts have cautioned that the Delta variant may soon become predominant in the US, and according to Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, this could probably be within weeks in undervaccinated areas. The CDC data suggest that the Delta variant may already be accountable for over 1 in 5 new COVID cases... (CNN)

Statins Tied to Lower Cancer Rate in Heart Failure Patients

Statins may have a role in preventing cancer, suggests a new study published online in the *European Heart Journal*. The study included around 800 patients with heart failure and noted that the patients who took statins had a significant reduction in the risk of developing cancer or of dying from cancer. According to the study, there was a 16% reduction in the incidence of cancer and a 16% reduction in cancer deaths among patients who took statins compared to those who did not take statins, reported researchers. This study is the largest one to evaluate the effects of statins in heart failure patients and the first major study to look for cancer-related outcomes in heart failure... (Medscape)

Emotional Management

When someone is doing something or is about to do something, in a way we don't want it to be done and we are not able to accept it, we become angry.

When someone is doing something or is about to do something, in a way we don't want it to be done, but we are able to accept it, we tolerate it.

When someone possesses something which we don't have, or someone produces the results which we are not able to produce, and we are not able to accept it, we become jealous.

When someone has something which we don't have, or someone can produce the results which we are not able to produce and we are able to accept it, we get inspired.

The emotional equation is simple.

Something + Acceptance = Positive Emotion

Something + Nonacceptance = Negative Emotion

'Something' or 'someone' is not making us feel positive or negative, our own 'acceptance' or 'nonacceptance' is giving rise to the positive or negative emotion.

It's not the world but our response to the world that determines the quality of our emotions.

Next time, don't ask who or what is disturbing you. Instead, assess who or what you are not accepting which is the reason behind this disturbance in you.

Replacing nonacceptance with acceptance turns the negative emotion into a positive one.

Emotional management involves stopping to blame 'something' or 'someone' and responding to life with 'acceptance'.

■ ■ ■ ■

First COVID Case could have Appeared in China in October 2019

According to a new study, the SARS-CoV-2 virus could have started spreading in China around October 2019 which is 2 months before the first case of COVID-19 was detected in Wuhan.

Investigators from the University of Kent employed methods from conservation science and estimated that the virus first emerged between early October and mid-November 2019. They estimated that the most probable date for the emergence of the virus appears to be November 7, 2019 and that the virus had likely spread globally by January 2020. The first official COVID-19 case in China was reported in December 2019 and was associated with Wuhan's Huanan seafood market. But it seems that some early cases had no known link with Huanan, which indicates that the virus was already in circulation before it reached the market. The findings are published in *PLOS Pathogens*... (Reuters)

Delta Variant may Outwit Even Fully Vaccinated Individuals, Say doctors

Experts have cautioned that COVID-19 could end up being more severe for people affected during the anticipated third wave, including for the 50% of third-wave patients who would be fully vaccinated. This could be attributed to mutations such as the Delta and Delta Plus.

However, the third wave could be much shorter than the second one, with fewer people contracting the infection. Experts are concerned that the mutations, first identified in India, could neutralize the protection provided by the vaccines during the upcoming wave, which will likely hit by September-October.

Raja Dhar, Director of Pulmonology at CMRI, said that variations of the virus occur due to mutations that take place regularly during a prolonged pandemic. He added that they are more potent than the existing ones and the third wave will likely include these... (ET Healthworld – TNN)

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Lighter Side of Medicine

HUMOR

Q: What do farmers use to make crop circles?

A: Pro-tractor!

Q: Why do cows like being told farmer jokes?

A: Because they like being "amooosed."

Tom: I've been stung by a wasp, have you got anything for it?

Nurse: Oh Lord! where is it?

Tom: I don't know. It could be miles away by now.

Three old, retired men were playing golf. All 3 had hearing loss as they got older.

First man: Windy, isn't it?

Second man: No, it's Thursday.

Third man: So am I. Let's have a juice!

Two carpenters, Jack and Tim, are working on a house. Jack is nailing down the timber; he keeps reaching into his nail pouch for nails, and every time he pulls one out, he either throws it over his shoulder or nails it in.

Tim is intrigued by this and eventually asks Jack, "Why do you keep throwing those nails away?"

Jack replies, "If I pull a nail out of my pouch and it's pointed toward me, then I throw it away because it's defective. If it's pointed toward the house, then I nail it in!"

Tim, equally stupid as Jack, yells at him, "You idiot! The nails pointed toward you aren't defective! They're for the other side of the house!"

My friend told me how electricity is measured, and I was like "Watt!"

Q: Why shouldn't you fall in love with a pastry chef?

A: He'll "dessert" you!

Q: Why do chemistry professors like to teach about ammonia?

A: Because it's "basic" material!

Lily: Mom, I want a new tutor.

Mom: Why is that?

Lily: Because the current tutor doesn't know any answers, and she keeps asking me for it!

Q: Why did the math textbook visit the guidance counselor?

A: It needed help figuring out its problems!

Q: What did the shark say when he ate the clown fish?

A: This tastes a little funny!

Dr. Good and Dr. Bad

SITUATION: A 54-year-old male with type 2 diabetes had morphological changes in erythrocytes as revealed by atomic force microscopy (AFM) findings (decreased concave depth, diameter, height and a deformation index and increased axial ratio, stiffness, adhesive force, aggregation and rigidity index). He was concerned whether this could be harmful or not?



LESSON: The researchers have shown that morphological changes in erythrocytes could lead to cardiovascular events, which are considered major complications of type 2 diabetes. Moreover, they showed AFM to be an excellent method for assessing altered erythrocytes of people with type 2 diabetes.

Micron. 2018;105:11-7.



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Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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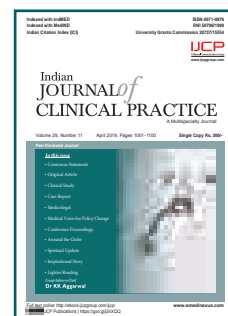
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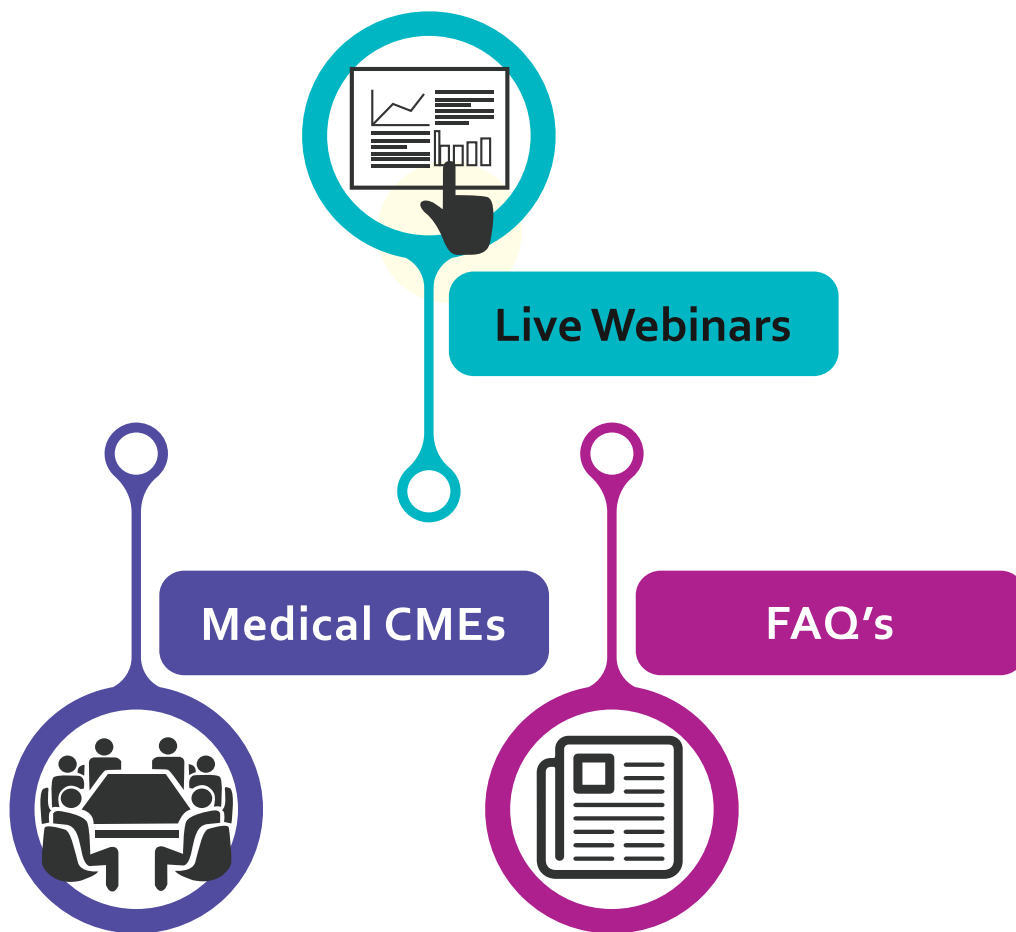
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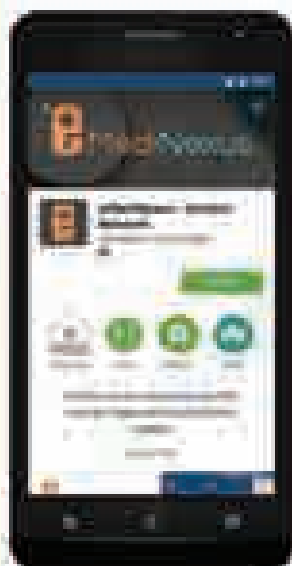
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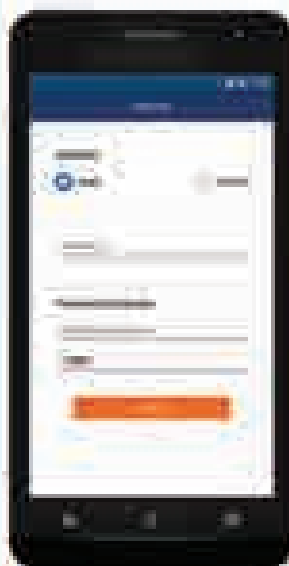
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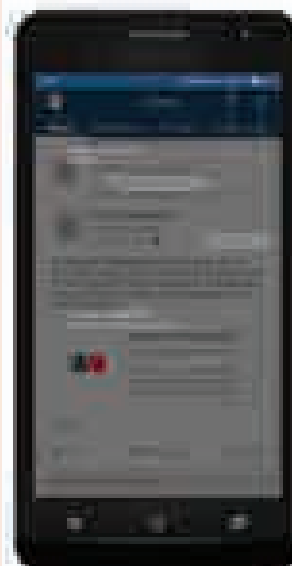
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