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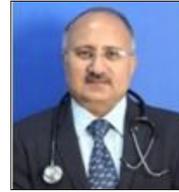
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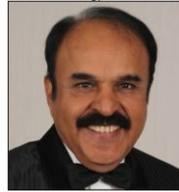
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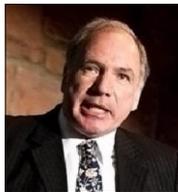
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Psychological Impact of Movement Control Order during Covid-19 Pandemic among Malaysian Population : An Online Survey — *Saravana Kumar, Supratik Chakraborty, Vijayabanu U, Gayathri Devi, Jothi Priya, Khin Than Zin, Saeid Reza Doust Jalali, Pricilla Das*

[Coronavirus 2019 Disease widely called as COVID-19 is an infectious disease-causing extreme containment measures, including strict Movement Control Order (MCO), travel ban, social distancing and strict personal hygiene. These act as stressors and tremendously affect the mental. This study investigates psychological impact of MCO during COVID-19 pandemic among Malaysian population.]

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Clinical Vignettes of Scrub Typhus Meningitis — *Satyabrata Ganguly, Sayonee Das, Ramiz Islam*

[Scrub Typhus with neurological manifestations are often described. We present here series of five cases of neurological manifestations in the form of meningitis in patients with Scrub Typhus.]

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An Observational Study on the Special Characteristics of Cardiovascular Manifestations of Systemic Lupus Erythematosus in North Eastern India — *Chitralkha Baruah, Abhrajyoti Biswas, Subhajit Mitra*

[Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with high prevalence of Cardiovascular abnormalities detectable with high-sensitivity imaging modalities. Introduction of Echocardiography has disclosed a higher prevalence of clinically silent patients with cardiac abnormalities.]

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A Study of Correlation Between Anthropometric Measurements and Carotid Intima Media Thickness in Newly Diagnosed Type 2 Diabetes Mellitus Patients in a Tertiary Care Hospital in Eastern India — *Himadri Shekhar Mondal, Prabir Kumar Kundu, Arindam Nag, Debasish Dey, Atanu Chandra, Apurba Kumar Mukherjee*

[The objective of the study was to find out correlation between Body Mass Index (BMI) and Waist Circumference (WC) with Carotid artery Intima Media Thickness (CIMT) in newly diagnosed Type 2 Diabetes Mellitus (DM) patients (within six month of initiation of antidiabetic drugs).]

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A Pilot Study to Assess the Impact of Zinc Hyper-supplementation on Hospital Stay of COVID-19 Patients — Results of a prospective Controlled Study — *Amrit Manik Nasta, Ramen Goel, Behram Pardiwala, Kedar Toraskar, Anish Desai*

[Zinc has been hypothesized to have antiviral benefits and a proposed preventive and therapeutic modality for COVID-19. There are no trials reporting the impact of Zinc supplementation on outcomes of hospitalized COVID-19 patients in India.]

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[COVID-19 Pandemic has shaken the world since Jan 2020 and countries are struggling now with second wave peaking in eastern nations while vaccine drive is going on in the western world. Exposure to the SAR2 CoV causes multisystem disease and not limited to lungs and airways.]

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Circumcision : Myths and Facts — *Amit Kumar, Bindey Kumar, Rashi Rashi, Ram Jeewan, Amit Kumar Sinha, Md Mokarram Ali*

[Since time immemorial one of the commonest surgery performed in the History of Mankind is Circumcision. The medical indications with sociocultural overlay surrounds it as a mysterious entity. This age old practice has been re-evaluated in the light of evidence regarding its relevance and usefulness in today's practice.]

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Autoimmune Encephalitis (Anti NMDA receptor Antibody Encephalitis) — Our Experience — *Ramya N, Goutami Priyadarsani, Sowmini P R, Sathish Kumar M, Malcolm Jeyaraj K, Sakthivelayutham S, Viveka Saravanan R, K Mugundhan*
[Autoimmune Encephalitis is an immune mediated Neurological Disorder which was recognized only in the 21st century. Neuroimmunology is one arena of Neurology which is amenable to effective management if identified early. There are many types of Autoimmune Encephalitis with unique clinical manifestations.]

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Physician's Role — The Challenging Task of Balancing Multiple Responsibilities — *Samik Kumar Bandyopadhyay*
[A doctor in the new millennium must engage in a host of activities other than direct clinical care. These include administrative responsibilities as a leader or a manager, teaching roles for students, trainees and the society and an effective communicator at large.]

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CHAUDHURI**

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Editorial

Health and Hamlet

India lives in the villages – is a common saying and as it happens with all common things, a gross aloofness and indifference develops against such things leading to its subtle yet rapid degradation. Rural health care is one such sector which languishes under such inadequacy of health care. While we as Indians preach fraternity and brotherhood and collectively believe in democracy inadequacy of health care in rural sector is a serious short fall. Rural Health care is one of biggest challenges facing the Health Ministry of India. With more than 70 percent population living in rural areas and low level of health facilities, mortality rates due to diseases are on a high.

Healthcare should be the right of every individual but shortage of quality infrastructure, lack of qualified health care workers, and non- accessibility to basic medicines and medical facilities restricts its reach to 60% of population in India. Approximately a majority of 700 million Indians live in rural areas where the condition of medical facilities is far below standard. There is an absolute need of new practices and procedures to ensure that quality and timely healthcare reaches the deprived corners of the Indian villages. Undoubtedly policies are there but they remain null and void due to lack of implementations. In rural India, where the number of Primary Health Care Centers (PHCs) is limited, 8% of the centers do not have doctors or medical staff, 39% do not have lab technicians and 18% PHCs do not even have a pharmacist. India also accounts for the largest number of maternity deaths. A majority of these deaths are in rural areas where maternal health care is poor. Even in private sector, health care is often confined to family planning and antenatal care and do not extend to more critical services like labor and delivery, where proper medical care can save life in the case of complications¹.

Contagious, infectious and waterborne diseases such as diarrhoea, amoebiasis, typhoid, infective hepatitis, worm infestations, measles, malaria, tuberculosis, whooping cough, respiratory infections, pneumonia and reproductive tract infections dominate the morbidity pattern, especially in rural areas. However, non-communicable diseases such as cancer, blindness, mental illness, hypertension, diabetes, HIV/AIDS, accidents and injuries are also on the rise. The health status of Indians, is still a cause for grave concern, especially that of the rural population. This is reflected in the high infant mortality rate (Fig 1)², high maternal mortality rate³; however, over a period of time some progress has been made. To improve

the prevailing situation, the problem of rural health is to be addressed both at macro (national and state) and micro (district and regional) levels. This is to be done in an holistic way, with a genuine effort to bring the poorest of the population to the centre of the fiscal policies. A paradigm shift from the current 'biomedical model' to a 'sociocultural model', which should bridge the gaps and

improve quality of rural life, is the current need. A revised National Health Policy addressing the prevailing inequalities, and working towards promoting a long-term perspective plan, mainly for rural health, is imperative⁴.

The above discussion clearly showcases the dire condition of rural health in India and we are well aware of it even before reading this article. However something must be done urgently to rectify the situation and to reach out to those population who are in absolute need to get proper healthcare at a proper time. But what are the barriers to health promotion and disease prevention in rural areas.

Higher poverty rates, Cultural and social norms surrounding health behaviours, Low health literacy levels and incomplete perceptions of health, Linguistic and educational disparities, Limited affordable, reliable, or public transportation options, unemployment, Lower population densities in certain areas for program economies of scale coverage, and effective program operation, Lack of access to nutritional food, Safe Drinking water, proper Sanitation Facilities are some of the many barriers.

According to Lancet India Group for Universal Healthcare, "To sustain the positive economic trajectory that India has had during the past decade, and to honour the fundamental right of all citizens to adequate health care, the health of all Indian people has to be given the highest priority in public policy. We propose the creation of the Integrated National Health System in India through provision of universal health insurance, establishment of autonomous organisations to enable accountable and evidence-

Trends in under-five mortality rate in India

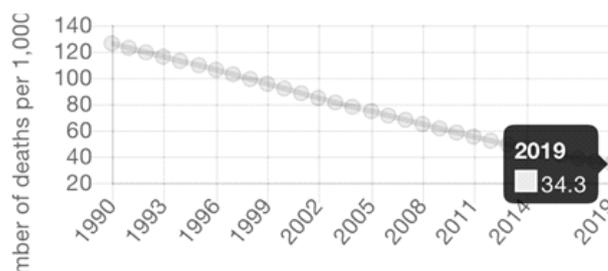


Fig 1

based good-quality health-care practices and development of appropriately trained human resources, the restructuring of health governance to make it coordinated and decentralised, and legislation of health entitlement for all Indian people. The key characteristics of our proposal are to strengthen the public health system as the

primary provider of promotive, preventive, and curative health services in India, to improve quality and reduce the out-of-pocket expenditure on health care through a well regulated integration of the private sector within the national health-care system. Dialogue and consensus building among the stakeholders in the government, civil society, and private sector are the next steps to formalise the actions needed and to monitor their achievement⁵.

Hitherto we have showcased a genre of problems which strangle the rural health infrastructure but finding ways out of it should also be a part of the discussion. Some possible ways out are discussed as below.

Various experts and practitioners, based on their own experience and global evidence, made the following recommendations that would have relevance for strengthening primary healthcare in rural India.

Investments in Primary Healthcare :

The policy commitment to invest 2.5% of GDP on healthcare and 70% of this expenditure on primary healthcare should be tracked periodically.

States that provide lower allocations on healthcare should be encouraged and supported to provide higher allocations.

Primary healthcare :

PHCs and Health and Wellness Clinics should retain the gatekeeping function:

This would help in increasing utilization of PHCs and maintain the primacy of primary healthcare. It would also help in reducing expenditure by reducing unnecessary referrals

There must be universal coverage for primary healthcare, in addition to the secondary and tertiary care:

Promoting access to primary healthcare will reduce the overall expenditure on healthcare, by reducing unnecessary referrals, by preventing illnesses, and by treating diseases at an earlier stage.

PHC team for health and wellness :

Responsibility (and accountability) for care of a defined population should be entrusted to the entire primary healthcare team:

The team would consist of the PHC staff (including the primary care physician), and H and WC staff (consisting of the mid-level provider, auxiliary nurse midwife (ANMs), multipurpose worker (MPWs), and accredited social health activists (ASHAs). Such a team is likely to provide comprehensive and continued care. Primary care physician should be trained in family medicine, and nurses (and other mid-level providers) should be trained in equivalent generalist care

Primary care team should be adequately supported through regular skilling, incentives, and supervision. Appropriate technological solutions should be provided to help them deliver quality healthcare. These teams should have functional linkages with higher levels of healthcare.

Creating and retaining healthcare professionals for rural primary healthcare (PHCs and H and WCs)

Revise undergraduate medical and nursing curriculum to align with rural priorities:

The training of MBBS should be aligned toward producing rural family physicians, and of nursing graduates, to produce rural primary care nurses

Currently, the graduate training of nurses and doctors has a heavy urban and tertiary healthcare bias

Allocate a large proportion of postgraduate seats for family-centered care with rural immersion:

In recent years, there has been a huge increase in postgraduate seats (MD/MS) for medical graduates. Allocating them to family medicine, with appropriate training in rural health care settings, will bring about the change in focus from tertiary care to primary care, and from urban bias to rural focus. It would require setting up family medicine programs in medical colleges, with strong rural focus

A similar shift can happen if large numbers of postgraduate seats for nurses are allocated to community health nursing, or nurse-practitioner program.

Make newly setup rural medical colleges responsible for district healthcare:

A large number of state-funded medical colleges are being set up in district hospitals, most of which are rural. Entrusting them with healthcare of their respective districts, focusing on sourcing rural students, adapting their training curricula to meet local needs, and helping them place within the districts would help them fulfil their social accountability. In such colleges, focus should be on primary and secondary care rather than tertiary care

Identify and accredit rural training sites for rural health professionals:

It would ensure sustained and high-quality training of a large number of professionals required for managing PHCs and H and WCs. The staff of these training sites should be accorded a faculty status.

Set up an empowered group to define improvements in training, living, and working conditions for rural healthcare professionals:

Such a group should be constituted of medical and nursing educationists from institutes that have a long experience of training doctors and nurses for rural areas, and practicing rural physicians and nurses⁶.

To conclude, we have to traverse a lot of ragged terrain before we reach the zenith of success equating the standard of health care available both in rural and urban sector. Indomitable zeal and incessant and conjoined efforts on behalf of the government as well as the health care professionals can slowly yet surely bring about the coveted sun rise in the comparatively darker valley of rural health care.

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Original Article

Psychological Impact of Movement Control Order during COVID-19 Pandemic among Malaysian Population : An Online Survey

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Background : Coronavirus 2019 Disease widely called as COVID-19 is an infectious disease-causing extreme containment measures, including strict Movement Control Order (MCO), travel ban, social distancing and strict personal hygiene. These act as stressors and tremendously affect the mental. This study investigates psychological impact of MCO during COVID-19 pandemic among Malaysian population.

Materials and Methods : Wakefield Inventory Scale is a self-report questionnaire consisting of twelve items were used to measure the occurrence and intensity often associated with depression. The questionnaire was made available online for three days and circulated through WhatsApp, only those who agree the consent form could take up the survey. The inventory was completed by 536 individuals participated in a study on depression outcomes via Google Doc, Online Survey as self-rated scale.

Results : Over all data suggested that more than 73% of the individual scored high which means they are in depressed state. Our sociodemographic data suggest that females experienced a more psychological impact of the outbreak. Majority of them feel that they are miserable, sad, frightened and panic during the pandemic. Around 50% of them still enjoy the things what they do at home and they get off to sleep easily without any pills but feels that they wake up early and then sleep badly for rest of the night.

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Key words : Depression, Mental health, COVID-19, Wakefield scale, Self-report.

Every human being strives for growth and well-being. More than physical well-being, psychological well-being decides the growth of the people¹. During the period of uncertainty, it's hard for even the strongest person to strive. COVID-19 had created one such uncertainty where individuals developed mental health issues including fear, anxiety and depression. Most of the people undergo psychological distress. Psychiatric disorders such as depression and anxiety have a strong impact on the Mental health status. Depression is the most common psychiatric morbidity that can be diagnosed among all the age groups and

Editor's Comment :

- COVID-19 pandemic is a public health disaster. Studies reveal that the MCO due to pandemic negatively affects depression among Malaysians.
- Awareness and knowledge about its effects and risk factors for depressive symptoms possibly help the people to overcome such situation.
- Health professionals should provide various initiatives to support psychological and mental health issues in order to manage the impact of the COVID-19 pandemic.

is often undiagnosed and underrated. Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute Respiratory Syndrome coronavirus 2 (SAR-CoV-2)². Since the early reports of COVID-19 cases in Wuhan, China in December 2019, the disease has spread too many parts of World like a wild-fire with no cure or vaccine to this end. On 11 March, 2020, the World Health Organization (WHO) declared COVID-19 as a Worldwide Pandemic.

Globally, several countries have imposed travel bans and lockdown, to contain the disease and Malaysia is no exception. The Movement Control Order (MCO) enforced by the Malaysian Government effective 18th March, 2020 has brought about a huge impact on the country in many ways. The nationwide Movement Control Order (MCO) has resulted in enormous economic losses and most of the activities in many industries have come to a halt during the MCO. It is

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believed that the disruptions will influence the mental health due to higher level of stress, anxiety and depression³. It is expected to have a long-term effect also. Intolerance of uncertainty leads to cognitive acceptability of the situation and people would start applying it to future events also^{4,5}. Research reviews were suggestive of the fact that uncertainty is one of the causes for depression. Most of the published literatures have focused on the epidemiological, pathological, clinical and pharmacological aspects of COVID-19 and not on psychological aspect⁶. Hence, the present study intended to explore the psychological aspect and the mental impact of COVID-19 among the Malaysian population.

MATERIALS AND METHODS

There are various scales used to measure the depression. However, Wakefield Inventory Scale is based on Zung's Scale has 12 items based on independent study which examined which of the Zung Scale items were most responsive to change in severity. The Wakefield Self-Report Questionnaire (Table 1) is scored by adding up the numbers selected for each of the 12 items. These items are labelled with Alphabets A to L. Calculations was done by scoring. Scoring for each question except 2, 5, 7 is zero points for No, not at all, 1 point for No, not much, 2 points for Yes, sometimes and 3 points for Yes, definitely. Whereas scoring for questions 2, 5, 7 is zero points for Yes, definitely, 1 point for Yes, sometimes, 2 points for No, not much, 3 points for No, not at all. Most depressed people score 15 or above on the Wakefield, because most non-depressed people score between 0 and 14. It is important to understand that a rating scale such as the Wakefield does not make a diagnosis on clinical depression. The Wakefield measures the frequency and indications often associated with depression. Some high scores may be accomplished by people with other emotional difficulties or physical disabilities. The

questionnaire was made available online for three days and circulated through WhatsApp, only those who agree the consent form could take up the survey. Wakefield self-assessment depression inventory was completed by 536 people participated in a study on depression outcomes via google doc, online survey as self-rated scale.

RESULTS

The calculation of the results was done by summing the scores that everyone has got. Over all data suggested that more than 73% of the individual scored 15 and above. When considering the importance of each, Item A reveals 42% of the people feel that they feel miserable and sad. Item B reveals same percentage feels sometimes they find it easy to do the things that they do. Item C reveals 35.8% feels frightened and panic (Fig 1). When we analyse the Item D, 47% of the individual feels they don't feel weeping spills and Item E reveals more than 50% still enjoy the things that they do. Item F reveals around 40% that is higher group of people feels that they are restless and can't keep still (Fig 2). Analysis of Item G shows that 71.6% individual feels they can get off to sleep easily without tablets. Item H reveals 40% of them do not feel anxious when they go out of the house. Item I show around 40% of them feel they lost interest in things either always or sometimes (Fig 3). Item J reveals around 47.5% feels tired of no reason. Item K shows 37% feels they are not more irritable whereas item L reveals around 40% of them feels that they wake up early and then sleep badly for rest of the night (Fig 4).

DISCUSSION

Coronavirus Disease (COVID-19) is a pandemic Global Health Warning. Within the few weeks of its epidemic the number of infected cases and deaths exceeded tremendously. In Malaysia, its outbreak was first revealed in late January, 2020. COVID-19 was first spotted on 25th January in the travellers from China arriving via Singapore. In the same month, the World Health Organization (WHO) declared the COVID-19 outbreak a public wellbeing emergency of International concern⁷. In Malaysia the cases remained relatively at a low level until localised clusters began to emerge in March, 2020. Symptoms of infection include fever, chills, cough, sore throat, breathing difficulty, myalgia, nausea, vomiting and diarrhoea. In severe cases it leads to respiratory failure, acute respiratory distress syndrome and death^{8,9}.

In response to the outbreak, the Malaysian Government has imposed a Movement Control Order starting from 18th March for two weeks, with travel

Table 1 — *The Wakefield Self-Report Questionnaire*

■ I feel miserable and sad.
■ I find it easy to do the things I used to do.
■ I get very frightened or panicky feeling for apparently no reason at all.
■ I have weeping spells or feel like it
■ I still enjoy the things I used to.
■ I am restless and can't keep still.
■ I get off to sleep easily without sleeping tablets.
■ I feel anxious when I go out of the house on my own
■ I have lost interest in things.
■ I get tired for no reason.
■ I am more irritable than usual.
■ I wake early and then sleep badly for the rest of the night.



Fig 1 — A is I feel miserable and sad; B is I find it easy to do things I used to do; C is I get very frightened for no reason

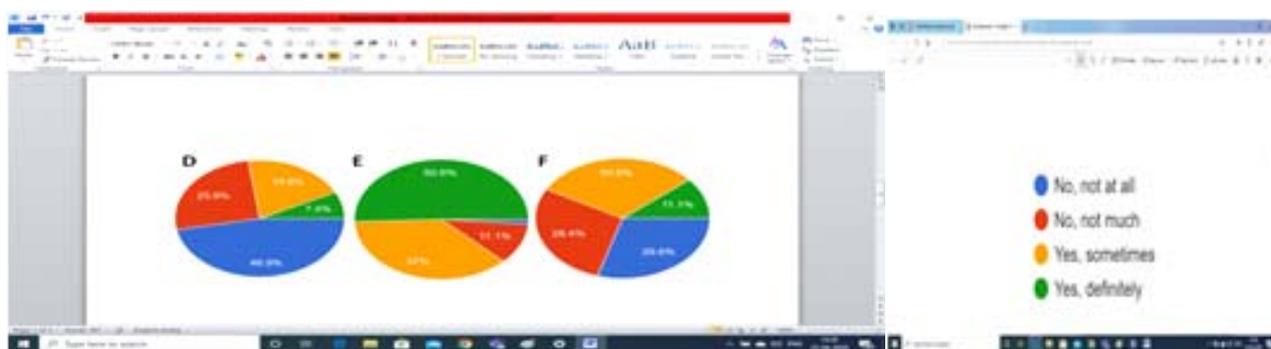


Fig 2 — D is I have weeping spells or feel like it; E is I still enjoy the things I do; F is I am restless and can't keep still



Fig 3 — G is I get off to sleep easily without sleeping tablets; H is i feel anxious when I go out of the house; I is i have lost interest in things

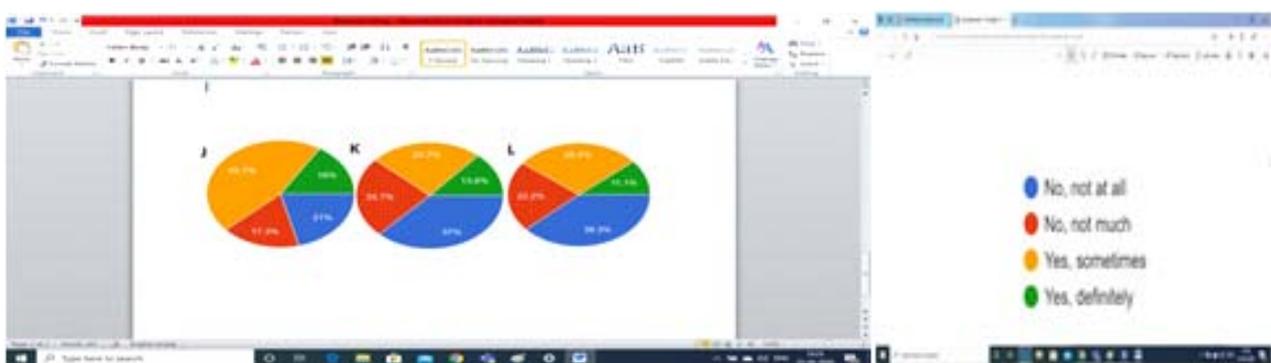


Fig 4 — J is I get tired for no reason; K is i am more irritable than usual; L is i wake early and then sleep badly for rest of the night

restrictions to control the spread of infection. Within days, the quarantine was extended to another one month¹⁰. Many stayed at home and socially isolated themselves to prevent being infected, leading to a desperate plea. Fear and worry about a disease can be tremendous and cause strong emotions in adults and especially children. How people respond to the outbreak can depend on their background. People who may respond more sharply to the stress of a crisis include older people with chronic diseases, children and teens, working persons financially, health care providers and people who have mental health conditions including problems with substance use^{11,12}. So, in our study we focussed on the teenagers and working persons, so we selected the age groups between 18 to 35 years. Another reason is that they are more accessible to electronic instruments for online survey.

In this study Wakefield self-assessment inventory scale was used as it can measure the depressive which was already used in a study to assess the severity of primary depressive illness¹³. Our study reveals that majority of the people feel miserable, sad, frightened and panic during which means during the movement control with less or no exposure to the outside made them emotionally weak, which also contributed to their mental health. Similar to our study, it was suggested that Government need pay more consideration to mental health problems, especially related to depression and anxiety problems among general population while fighting during public health emergency^{15,16}. However, in our survey majority of them still enjoy the things what they do at home and they get off to sleep easily without any pills but feels that they wake up early and then sleep badly for rest of the night which is the clear sign of disturbed sleep, that leads to depression as described earlier that sleep disorders are the core symptoms of depression^{11,14}.

To conclude our findings, show there is more prevalence of mental health problems that are more likely to be associated during the COVID-19 outbreak. Malaysian Government need pay more interest to Psychological Health among general population at the same time as battling with COVID-19.

Ethical clearance- Since the data collection was not done in any organisation or institutional ethical clearance was not obtained. However, confidentiality of the participants was maintained as no questions reveal their identity was asked. Participants were explained about the research only those who agree the consent form could take up the survey. Rights of participants were preserved. Data obtained from them

was used only for the research purpose.

Source of Funding : Self

Conflict of Interest : NIL

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Original Article

Clinical Vignettes of Scrub Typhus Meningitis

Satyabrata Ganguly¹, Sayonee Das², Ramiz Islam³

Aim : Scrub Typhus with neurological manifestations are often described. We present here series of five cases of neurological manifestations in the form of meningitis in patients with Scrub Typhus.

Background : Scrub Typhus is an endemic disease in India caused by *Orientia tsutsugamushi*, transmitted by trombiculid mites. It is an important cause of acute febrile illness in India. Signs & symptoms include fever, headache, myalgia & GI symptoms & is generally associated with morbilliform rash (<40%), eschar (<50%) which is due to bite of the mite. Abnormal LFTs & lymphocytosis are commonly seen in early phase of illness. It's often labelled as Pyrexia of Unknown Origin (PUO). Early diagnosis & prompt administration of therapy mostly leads to complete recovery.

Method : We screened patients presenting with fever, headache, neck stiffness, vomiting, photophobia and evaluated them for meningitis. Patients in whom no cause of fever could be established, having lymphocytosis, hyponatremia & transaminitis, they were tested for Scrub Typhus by using Indirect immunofluorescence & detection of IgM antibody.

Conclusion : This study will help clinicians to have a stronger suspicion of Scrub Typhus in undiagnosed febrile patients.

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Key words : Scrub Typhus, Rickettsia, Eschar, Hyponatremia, Meningitis.

Last summer (ie, 1877), I had the opportunity of observing a disease which, so far as I know, is peculiar to Japan and has not yet been, described. It occurs, moreover, in certain well-marked districts and at a particular season of the year, so that the opportunities of investigating it do not often occur. It is known here as the Shima-mushi, or Island-insect Disease and is so-named from the belief that it is caused by the bite or sting of some insect peculiar to certain islands in the river known as Shinagawa, which empties itself into the sea at Niigata.”
— Theobald Adrian Palm

To the Western World, first reported incident of Scrub Typhus was noted by a physician named Theodore Adrian Palm in the year of 1878, which was prevalent on the banks of Shinano River. However, a Japanese physician named Hakuju Hashimoto gave the medical description of the disease from Niigata prefecture in the year of 1808. The earliest record of the disease came from 3rd Century China. Name of the disease came from “tsutsuga” (fever, illness) and “mushi” (bug, insect). During the second world war in the Pacific theatre the disease become very prevalent and both the Allied and Japanese forces suffered a huge blow from Scrub Typhus and has even outnumbered weapon related casualties.

Scrub Typhus is an acute febrile illness caused by *Orientia tsutsugamushi* and is characterized by an

Editor's Comment :

- Though Scrub typhus is commonly encountered in patients either residing in hilly or forest areas or having a travel history to endemic areas, due to urbanisation and afforestation it is frequently found in urban areas nowadays. Rickettsial cause still remains an important differential diagnosis for patients presenting with meningitis testing negative for the commonly encountered causes.

eschar, lymphadenopathy, multisystem involvement and a rapid response to doxycycline. Scrub Typhus is seen in to the so-called Tsutsugamushi Triangle, a region covering the Russian Far East in the North, Japan in the East, Northern Australia in the South and Afghanistan in the West and is related mostly to agricultural activities¹. In our institute based on Southern Fringes of Kolkata receiving patients from both 24-Parganas which has primarily a rural background there has been an increased identification of Scrub Typhus as a cause of fever in ward. Some of these patients landed up with complications of meningitis and meningoencephalitis. We created a profile of 21 such patients of Scrub meningitis in our institute with their varied presenting feature, clinical course and lab parameters (Table 1, Fig 1).

Investigations revealed predominant peripheral lymphocytosis, hyponatremia, raised hepatic transaminases, raised acute phase reactants (Ferritin, LDH) (Table 2).

The patients were initially given Injection Ceftriaxone and Mannitol initially (Fig 2).

All infective profile (Malaria, Dengue, Typhoid) & Viral serology were negative.

On Lumbar puncture the opening pressures were high & Cerebrospinal Fluid (CSF) findings were noted (Table 3).

MR Venogram of few patients revealed cerebral

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Table 1 — Examination Findings

Patient No.	Sex	Age (Years)	Fever For Days	Eschar	Head-ache	Nuchal Rigidity	Myalgia	Altered Sensorium	Nausea/vomiting	Pulse rate	Hospital Stay (days)
1	Male	32	7	Yes	Yes	Yes	No	Yes	Yes	Bradycardia	8
2	Female	32	6	Yes	Yes	Yes	No	No	No	Bradycardia	10
3	Female	48	4	Yes	Yes	Yes	No	No	Yes	Tachycardia	7
4	Male	65	8	No	Yes	Yes	Yes	No	Yes	Bradycardia	12
5	Female	53	7	No	Yes	Yes	Yes	Yes	Yes	Tachycardia	8
6	Male	34	6	No	Yes	Yes	Yes	No	Yes	Tachycardia	9
7	Female	42	4	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	9
8	Male	58	3	Yes	Yes	Yes	Yes	Yes	Yes	Tachycardia	7
9	Female	52	7	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	6
10	Female	64	4	Yes	Yes	Yes	Yes	Yes	Yes	Tachycardia	12
11	Male	32	5	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	10
12	Male	22	4	Yes	Yes	Yes	Yes	No	No	Tachycardia	9
13	Female	56	4	Yes	Yes	Yes	No	Yes	No	Tachycardia	8
14	Female	44	7	No	Yes	Yes	No	Yes	No	Bradycardia	7
15	Male	29	7	Yes	Yes	Yes	Yes	No	No	Tachycardia	11
16	Male	18	4	No	Yes	Yes	No	Yes	No	Tachycardia	8
17	Female	35	6	No	Yes	Yes	Yes	Yes	No	Tachycardia	8
18	Female	43	5	No	Yes	Yes	No	No	No	Bradycardia	7
19	Male	51	6	Yes	Yes	Yes	No	Yes	Yes	Bradycardia	6
20	Female	58	7	No	Yes	Yes	Yes	No	Yes	Tachycardia	6
21	Female	27	7	No	Yes	Yes	No	No	No	Tachycardia	8

venous sinus thrombosis (involving Superior sagittal sinus, Straight sinus, right transverse sinus) (Fig 3).

Scrub typhus IgM (IFA method) were positive in all cases (Fig 4).

Hence, the patients were diagnosed to be of Scrub Typhus Meningitis.

They responded well to Doxycycline (100 mg q12h for 10-15 days). Sensorium improved within 2-3 days of starting therapy. Out of the 21 cases there were only 2 deaths reported.

MATERIALS AND METHODS

Type of study : Cross sectional study

Study setting : KPC

Medical College & Hospital, Jadavpur, Kolkata-700032

Place of study : Admitted patients in the Department of General Medicine, Intensive care unit in KPC Medical College & Hospital

Period of study : 8 months (May to December 2019)

Study population: Patients presenting with fever for more than a week.

Sample size : Out of all the patients being



Fig 1 — Eschars

Table 2 — Investigation Findings

Patient no	Hb Gm%	TLC Mil/cumm	PLC Lac/cumm	CRP mg/L	BIL mg/dl	AST U/L	ALT U/L	ALP U/L	ALB Gm/dl	CPK U/L	LDH U/L	Cr mg/dl	Urea mg/dl	Na+ mEq/L	K+ mEq/L
1	13.5	10700	1.10	24	0.8	77	68	406	3.6	650	1060	0.9	28	136	3.9
2	10.2	10200	0.87	48	2.1	87	68	187	3.2	700	887	1.2	44	131	3.4
3	11.6	8600	1.64	36	1.5	66	78	276	3.4	466	654	1.1	36	130	3.2
4	8.9	9800	1.26	24	1.2	66	89	238	3.0	864	746	1.2	48	128	3.2
5	12	12000	1.34	12	1.8	84	76	268	3.2	586	688	1.3	50	126	3.6
6	14	12600	1.38	24	1.4	64	78	300	3.0	458	564	1.4	48	131	3.7
7	12.2	8600	1.30	12	1.6	56	68	238	3.4	606	568	1.2	28	134	3.8
8	10.4	9800	1.10	48	1.2	64	78	342	3.0	678	688	0.9	32	130	3.8
9	9.2	12500	1.35	36	1.8	78	88	238	3.4	876	1060	1.2	34	138	4.0
10	10.6	8800	1.80	48	2.2	84	76	286	3.2	986	866	1.4	44	132	4.0
11	13.2	14000	1.4	64	2.4	78	88	284	3.4	678	776	0.8	32	126	3.8
12	14.4	11300	1.54	24	1.6	66	68	248	3.2	566	709	0.9	26	134	4.0
13	12.6	14300	1.27	48	2.4	67	86	308	2.8	877	823	0.8	34	136	3.8
14	11.2	12700	1.68	24	2.2	86	82	243	3.8	457	569	0.9	32	134	3.9
15	12.5	8750	1.90	12	1.4	76	78	268	3.6	866	788	1.2	34	138	3.8
16	11.8	9800	1.87	12	1.5	77	87	246	3.8	477	677	1.3	44	132	3.9
17	9.7	8800	1.65	12	1.4	76	86	286	3.4	662	568	1.2	32	130	3.6
18	8.4	7800	1.67	06	1.2	64	64	286	3.2	544	466	1.2	28	132	3.8
19	13.8	11400	1.38	12	1.7	46	54	179	3.2	566	658	1.3	36	134	3.4
20	10.8	12340	1.46	06	1.2	39	48	178	3.6	499	567	1.2	33	139	3.8
21	11.2	10400	1.65	12	1.4	68	56	188	4.0	563	876	1.3	34	135	4.2

NCCT Brain revealed diffuse cerebral oedema with effaced ventricles.

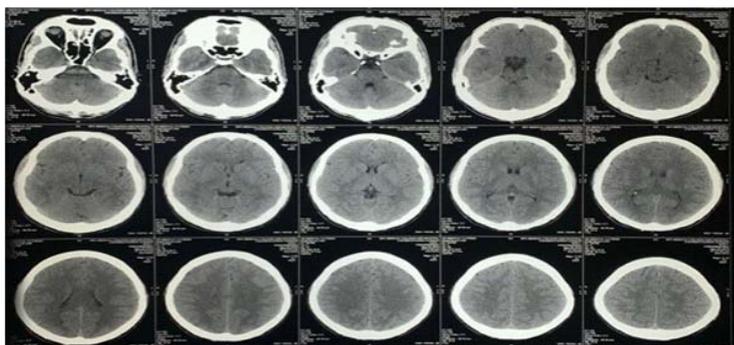


Fig 2 — NCCT Finding

Patient No.	Sex	Age (Years)	Cell count (cells/cu.mm)	Cell type	Protein (mg/dl)	ADA (U/L)
1	Male	32	50	Mononuclear cells	21	6.0
2	Female	32	20	Mononuclear cells	140	3.0
3	Female	48	4	Lymphocytes	122	5.0
4	Male	65	10	Mononuclear cells	22.7	6.4
5	Female	53	0	Acellular	135.4	3.0
6	Male	34	10	Mononuclear cells	22	4.0
7	Female	42	3	Lymphocytes	130	6.0
8	Male	58	2	Mononuclear cells	120	8.0
9	Female	52	0	Acellular	27	5.0
10	Female	64	0	Acellular	116	2.0
11	Male	32	22	Mononuclear cells	78	5.0
12	Male	22	10	Mononuclear cells	32	4.0
13	Female	56	5	Lymphocytes	122	8.0
14	Female	44	7	Mononuclear cells	44	6.0
15	Male	29	12	Mononuclear cells	60	4.0
16	Male	18	10	Mononuclear cells	51	5.0
17	Female	35	4	Lymphocytes	26	3.0
18	Female	43	2	Lymphocytes	140	10.0
19	Male	51	20	Mononuclear cells	84	2.0
20	Female	58	0	Acellular	124	3.0
21	Female	27	0	Acellular	132	2.0

admitted in KPCMCH with fever, during the study period, first 100 consecutive patients fulfilling the study criteria was selected for the study.

Selection criteria :

(1) Inclusion criteria —

- Patients admitted with fever but tested negative for commonly sent infective profile according to local guidelines for infectious disease (Eg: Dengue NS1 antigen, MP, MPDA, TyphidotM, viral serology).

- Patients with Pyrexia of Unknown Origin.

- Patients giving consent for the study.

(2) Exclusion criteria —

- Already diagnosed cases of fever on admission.

- Immunocompromised patients.

- Patients not giving consent for the study.

Test performed : Serologic assays, Scrub typhus IgM (Indirect Immunofluorescence Assay method) were performed for all the suspected patients.

Statistical analysis : Descriptive values were expressed as mean \pm standard deviation and percentage accordingly. The *p* values were two-tailed and those

<0.05 were considered statistically significant.

DISCUSSION

Scrub Typhus is acute febrile illness, caused by *Orientia tsutsugamushi* and is transmitted to humans by trombiculid mites. It is commonly seen during monsoon and post monsoon season in our country², causing lot of morbidities and occasional mortality. It involves all organ system of body³ commonly characterised by fever, rash, lymphadenopathy, myocarditis and pneumonitis. The most characteristic skin manifestation is *Eschar* which is seen in about 4%-46% in Indian population⁴. Neurological involvement, both Peripheral and Central Nervous System are well known⁵. Most common Central Nervous System (CNS) manifestation is Meningitis and Meningo-encephalitis; also seen are Cerebral Infarction, Cerebral Venous Sinus Thrombosis Acute Disseminated Encephalomyelitis (ADEM) and cranial neuropathies (mostly isolated)⁶.

It has varied presentation & is an important cause of morbidity & mortality. Common laboratory findings were normal or low WBC counts with predominant lymphocytosis, mild to moderate serum elevations of hepatic enzymes and hyponatremia. Hyponatremia is an important finding⁷ and was almost invariably found in all patients with Scrub Typhus.

After its re-emergence, Scrub Typhus has become an important cause of morbidity and mortality in patients presenting with febrile illness during monsoon and postmonsoon season². According to WHO, Scrub typhus is probably one of the most underdiagnosed and under-reported febrile illnesses requiring hospitalisation⁸. It is transmitted by bite of Trombiculid Mites during the season of activity or travel to or residence in an endemic geographic region during the incubation period (6-21 days)⁹. A clinician must possess high degree of suspicion for Scrub Typhus if a patient of febrile illness tests negative for all the common infective profile as per the local infection control guidelines. Though Scrub Typhus is commonly encountered in patients either residing in hilly or forest areas or having a travel history to endemic areas, due to urbanisation and afforestation it is frequently found in urban areas nowadays. Scrub Typhus was diagnosed in our patient by the presence of IgM antibody in serum. Neurological involvement in Scrub Typhus has been well documented in literature⁵. Meningitis/ meningo-encephalitis is the most common manifestation⁴ (15%-50% cases)¹⁰.

CONCLUSION

Scrub Typhus can present with variety of neurological manifestations. Scrub Typhus meningitis is a milder complication compared to Respiratory or Gastrointestinal problems even if it is associated with altered sensorium or cranial nerve deficits and generally resolves completely

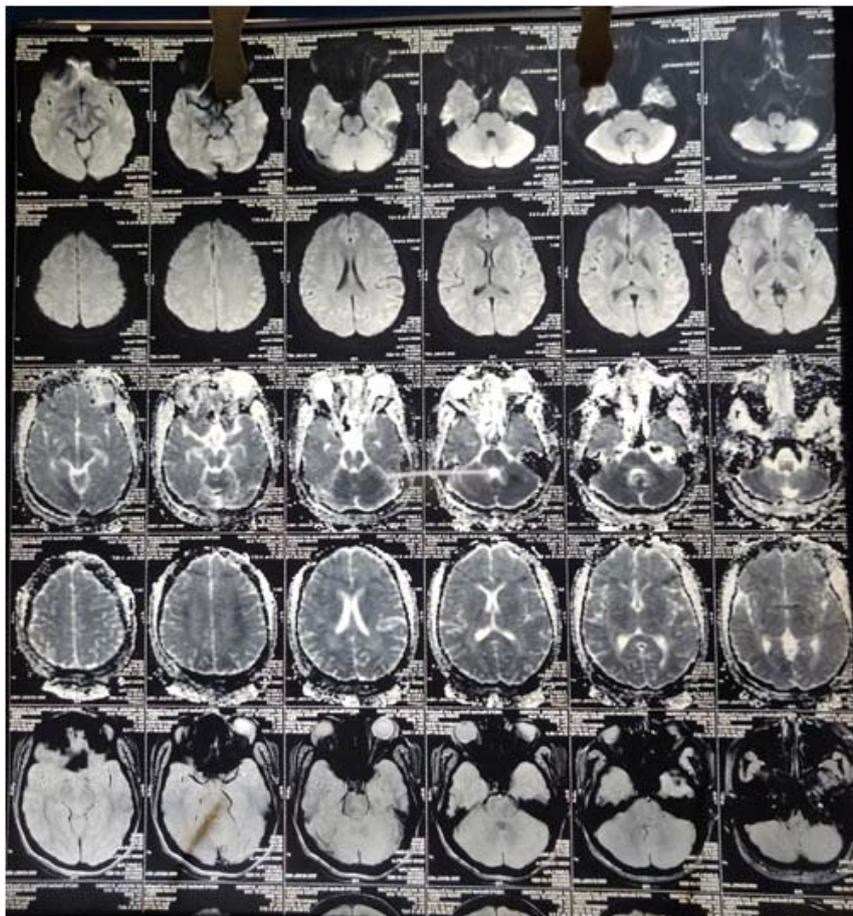


Fig 3 — MRI Brain suggested meningitis

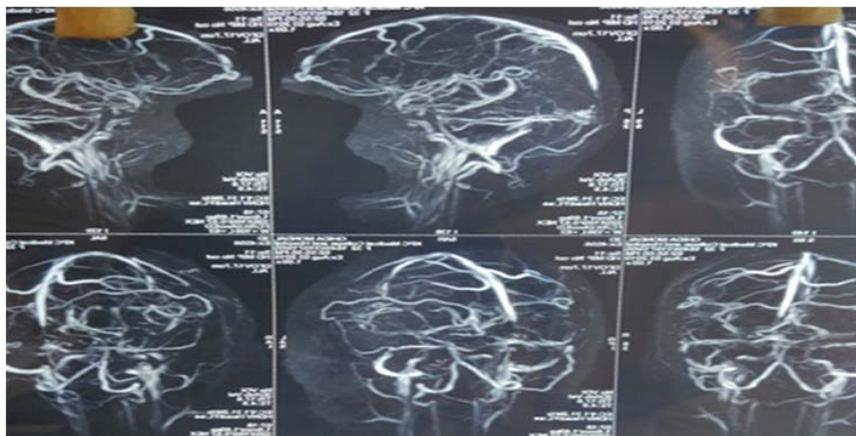


Fig 4 — MR Venogram

with Doxycycline Therapy. Due to the presence of lymphocytic pleocytosis with increased CSF protein, TBM is a close differential diagnosis. This may result in rifampicin-based ATT masking the diagnosis of Scrub Typhus and sometimes results in patients continuing long term therapy for TBM. Since India is endemic for both TB and Scrub Typhus, awareness of simple-to- treat

Scrub Typhus with access to specific tests like scrub IgM and Cerebrospinal Fluid (CSF) Adenosine Deaminase (ADA) may go a long way in avoiding unwarranted treatment in patients. Older age, longer duration of fever, thrombocytopenia, abnormal liver and renal function, hyponatremia and elevated C-Reactive Protein (CRP) levels are associated with severe complications and prolonged treatment duration. Clinically, younger patient population, rapid diagnosis, and prompt treatment may be associated with a shortened disease course and a better outcome. We should be vigilant so that proper diagnosis and management can be given in due time with satisfactory improvement.

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Conflict of interest : None

Ethical Approval : Taken

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Original Article

An Observational Study on the Special Characteristics of Cardiovascular Manifestations of Systemic Lupus Erythematosus in North Eastern India

Chitrallekha Baruah¹, Abhrajyoti Biswas², Subhajit Mitra³

Introduction : Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with high prevalence of Cardiovascular abnormalities detectable with high-sensitivity imaging modalities. Introduction of Echocardiography has disclosed a higher prevalence of clinically silent patients with cardiac abnormalities.

Aims and Objectives : To study the Cardiovascular manifestations and Echocardiographic changes in patients of Systemic Lupus Erythematosus.

Materials and Methods : A total of 82 Systemic Lupus Erythematosus patients aged more than 12 years were selected as per 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria. Clinical and Echocardiographic findings were evaluated.

Results : In our study, median age was 25.5 years and mean age 27.33±10.96 years. The most common Cardiovascular Manifestation was Hypertension in 22 (26.82%) patients amongst whom 15 (18.29%) patients had Echocardiographic evidence of Left Ventricular Hypertrophy. Pericardial disease was detected in 17(20.73%) cases clinically whereas Echocardiographic evidence was present in 26(31.71%) cases. Valvular abnormality was detected clinically in 9(10.97%) out of 82 cases although Echocardiography showed evidence in 31(37.8%) cases. Cardiomyopathy was found in 6.09% cases. Two (2) out of 8 male patients have evidence of Cardiomyopathy. It is also found to be more prevalent in female patients in ethnic groups. Hypertriglyceridemia and increased Very low-density lipoprotein (VLDL) were the most common lipid abnormality detected amongst SLE patients. No significant antibody association was seen in patients with Cardiovascular manifestations unlike Anti ds Deoxyribonucleic Acid (DNA) in Lupus Nephritis.

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Key words : Systemic Lupus Erythematosus, Cardiovascular manifestations, Echocardiography, Pericardial effusion, Valvular abnormality.

Systemic Lupus Erythematosus (SLE) is an Autoimmune disease that involves multiple organs of the body and has variable clinical presentations. The cells and organs undergo damage mediated by tissue binding autoantibodies and immune complexes. Prevalence frequencies of SLE range from 20 to 240 per 1,00,000 persons and reported incidence rates range from 1 to 10 per 1,00,000 person-years¹. The prevalence of SLE in India is comparatively low. Only 3 cases of SLE were detected in a population survey of 91,888, giving a point prevalence of 3.2 per 100,000². Demographic data has showed significant variations in the clinical manifestations of SLE between Eastern and Western parts of India³.

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Editor's Comment :

- Cardiovascular manifestations mostly remained silent in SLE.
- Echocardiography picked up evidence of cardiovascular disease in patients who were clinically silent.
- High index of suspicion and early use of Echocardiography may aid diagnosis and reduce mortality and morbidity in Systemic Lupus Erythematosus.

The description of cardiac involvement in SLE was first reported by William Osler in 1895. Cardiovascular manifestations of SLE can be divided into following: valvular and Pericardial Involvement, Myocardial Dysfunction, Conduction Disorders, Accelerated Atherosclerosis and Thromboembolic Disease. Cardiovascular Manifestation however, remain clinically unnoticed during life in majority of SLE patients⁴.

Introduction of two dimensional and Doppler Echocardiography has disclosed a higher prevalence of patients with Cardiac Abnormalities in SLE patients⁵.

Hence, this study on special characteristics of

Cardiovascular manifestations in cases of SLE with special reference to 2D Echocardiographic evaluation has been done with following Aims and Objectives.

AIMS AND OBJECTIVES

(1) To study the cardiovascular manifestations in patients of SLE.

(2) To study the association of clinical and echocardiographic findings in cases of SLE.

MATERIALS AND METHODS

The study was a hospital based cross sectional study conducted in the Department of Medicine at Gawahati Medical College and Hospital, Guwahati, Assam, for a period of one year extending from 1st June 2018 to 31st May 2019, following clearance from ethics committee. A total of 82 cases of SLE, both male and female, were taken up for the study. Statistical graphs were prepared using Microsoft Excel 2007 and Microsoft Word 2007. Statistical analysis was performed using GraphPad in Stat version 3.00 for Windows 7, Graph Pad Software, San Diego, California USA. (www.graphpad.com). Chi square test was used for analysis. P value < 0.05 was taken as statistically significant.

Inclusion Criteria :

(1) SLE patients (as per 2012 Systemic Lupus International Collaborating Clinic Criteria (SLICC criteria) who were above the age of 12 years

Exclusion Criteria :

- Age < 12 years
- Comorbidities like Diabetes Mellitus, Hypothyroidism and other autoimmune disorder.
- Sepsis in SLE
- History of alcohol and drug abuse.
- Cardiovascular diseases attributable to other causes like Congenital Cardiac Diseases, Rheumatic Heart Disease, Peripartum Cardiomyopathy, Hemochromatosis, Amyloidosis.
- Pregnancy

OBSERVATIONS AND RESULTS

The Median age was 26 years and mean age was 27.94 with a standard deviation of 10.54 years. Maximum number of cases were in the age group of 21-30 years. There were 8 male SLE cases while females were 74 making the Female to Male ratio of 9.25:1. The cases were more prevalent from rural areas (57%) whereas 43% of the patients were from urban areas.

Cardiovascular manifestations were clinically detected in 33 (40.24%) patients. The most common

Cardiovascular manifestation was Hypertension, present in 22 (26.82%) cases followed by Congestive Cardiac Failure in 15 (18.29%) cases and pericardial disease in 17 (20.73%) cases. Valvular Heart Disease were seen in 9 (10.98%) cases, Coronary Artery Disease in 6 (7.32%) cases and Arrhythmia in 4 (4.88%) cases.

The most common Echocardiographic finding was Valvular abnormality found in 31 (37.8%) cases, followed by Pericardial effusion/ pericarditis in 26 (31.71%) cases and Cardiomyopathy in 05 (6.09%) cases. The other significant abnormalities seen were : Diastolic Dysfunction 20 (24.39%) cases, Left Ventricular Hypertrophy 15 (18.29%) cases and Pulmonary Arterial Hypertension 4 (4.87%) cases, Regional Wall Motion Abnormality 7 (8.54%) and Global Hypokinesia 2 (2.44%) cases.

Echocardiography revealed Cardiovascular Disease in 46 (56.10%) cases of which 30 (36.58%) cases were diagnosed clinically and the rest 16 (19.51%) remained clinically silent.

Increased Triglyceride 33 (42.24%) was the most common lipid abnormality in this study amongst SLE patients, followed by Hypercholesterolemia (16 cases (19.51%) and raised VLDL (16 cases- 19.51%). Antinuclear Antibodies (ANA) (96.34%) and Anti ds DNA (47.56%) were among the most common serological markers seen in SLE patients in our study followed by Anti Sm (36.58%), Anti-nucleosome (31.97%), Anti Ribosomal P (31.71%) and Antiphospholipid Antibodies (APLA) was seen in 18.29% cases.

Amongst the 33 patients with Cardiovascular manifestations, 3 (9.09%) patients had no disease activity, 13 (39.39%) patients had mild disease activity, 7 (21.21%) patients had moderate disease activity, 5 (15.15%) patients had high disease activity and 5 (15.15%) patients had very high disease activity (Figs 1-6 & Tables 1-4).

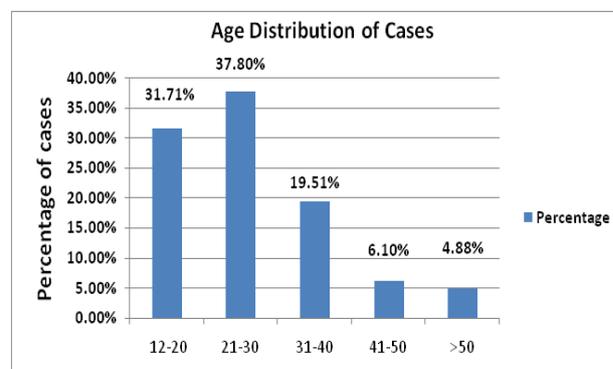


Fig 1 — Bar diagram showing age distribution of cases

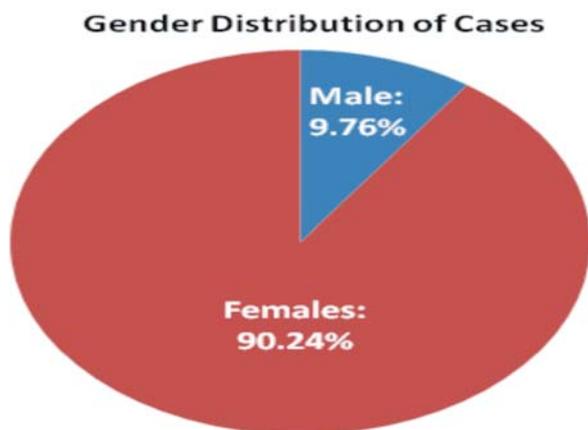


Fig 2 — Pie diagram showing gender Distribution of cases

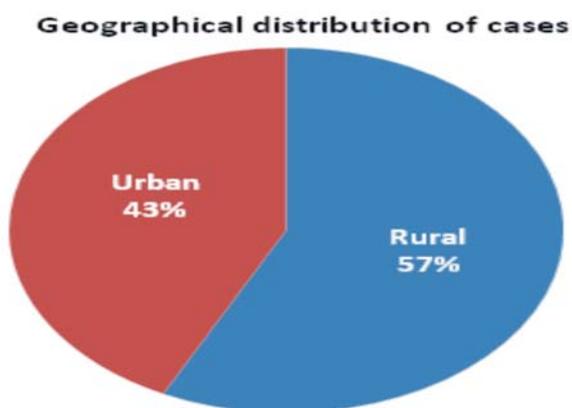


Fig 3 — Pie diagram showing Geographical distribution of cases

DISCUSSION

The Median age was 26 years and mean age was 27.94 with a standard deviation of 10.54 years.

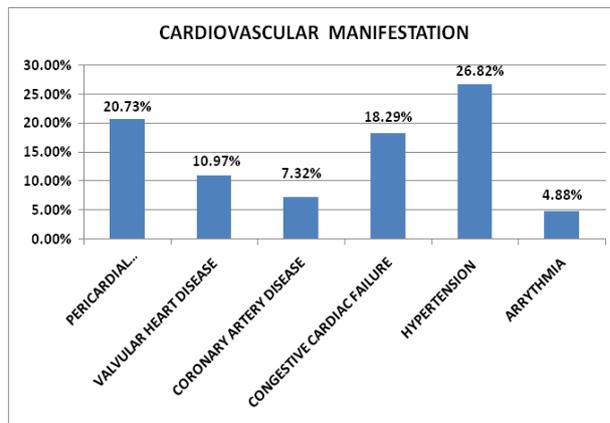


Fig 5 — Bar diagram showing clinical diagnosis of Cardiovascular Manifestation

Maximum number of cases was in the age group of 21-30 years. Other Indian studies which showed similar findings include Malaviya AN, *et al* (1988)⁴ and Vaidya S, *et al* (1997)⁵ where the peak incidence was seen in the 3rd decade. The Female to Male ratio was 9.25:1. Robert M, *et al* (2006)⁶ and Kakati S, *et al* (2017)⁷ reported a Female to Male ratio of 11.5:1 and 12:1 respectively.

Most of the cases were rural predominant (57%), more so in tribal populations of Assam. Gergianki I, *et al* (2019) showed that risk of SLE in urban population is 2.08 times more than rural²³.

In our study, Cardiovascular manifestations were clinically detected in 40.24% patients. Study conducted in different parts of India like Madhavan R, (1983), Malaviya AN (1985), Vaidya S (1997), Paul BJ (2003) and Seigal R (2011) found Cardiovascular manifestations of 9.2% of 54 patients, 5% of 101 patients, 11.8% of 220 patients, 5.3% in 75 patients

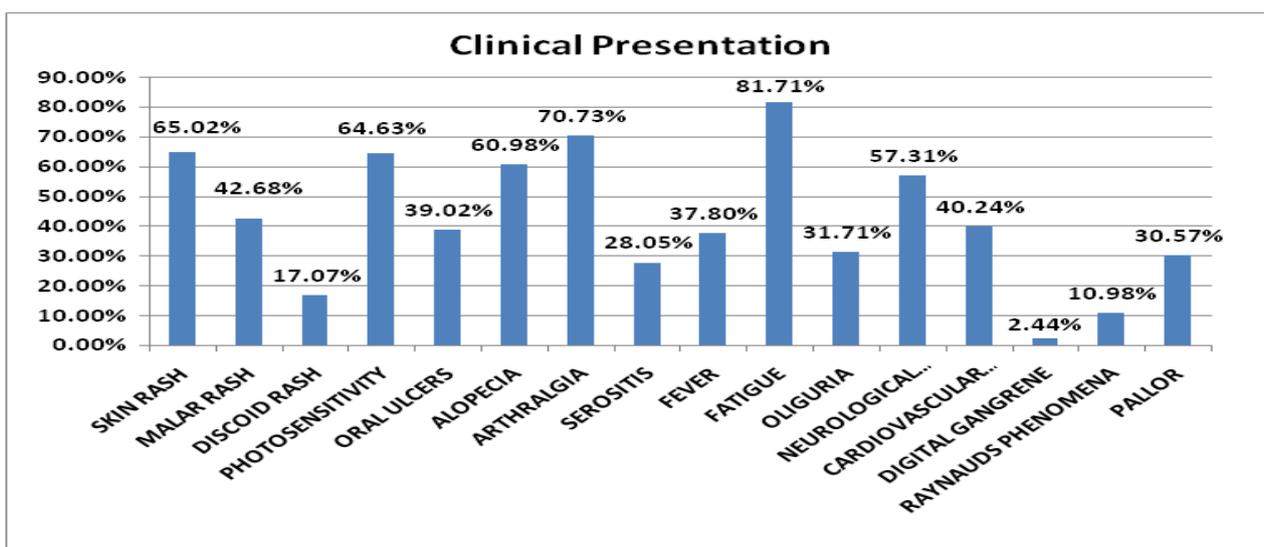


Fig 4 — Bar diagram showing clinical presentations of cases

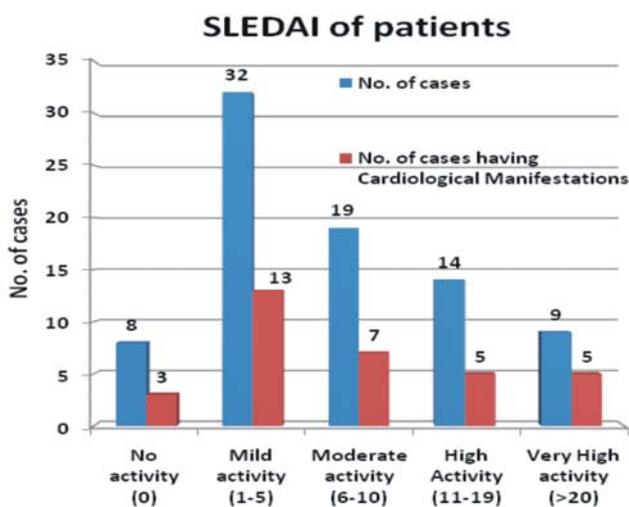


Fig 6 — Clustered Bar diagram showing SLEDAI of patients

and 6.7% of 60 patients respectively in patients of Systemic Lupus Erythematosus (SLE). However, a study by Harvey AN, *et al* (1954) found 55% out of 130 patients showed Cardiovascular involvement at some stage of their illness. Moder K G *et al* (1999) stated Cardiovascular involvement in 50% cases of SLE.

The most common Cardiovascular manifestation was Hypertension present in 26.82% cases. Hypertension was noted in 22%¹⁰ and 30.4%¹⁴ patients in different studies. The findings of these studies are almost consistent with the findings of our study. Few studies showed lower incidence of Hypertension in 14% and 4% of patients of SLE^{10,13}.

Congestive Cardiac Failure was present in 18.29% cases. Other studies reported Congestive Cardiac Failure in 7% and 5-31.0% patients of SLE^{8,14}. Pericardial effusion was clinically detected in 20.73% cases in our study. In a study in Spain pericardial effusion was clinically detected in less number of cases (7%)³. However, it was detected in higher number of cases (25.4%) in a meta-analysis by Chen J, *et al* (2006)¹⁵.

Valvular Heart Disease was present in 10.98% cases in our study. Clinically important valvular disease was found to be present in 16.7% and 13-65.0% cases of SLE which was slightly higher in comparison to our study^{12,14}.

The prevalence of Cardiovascular events like Myocardial Infarction, cardiac sudden death or Angina was reported in 8.3% in the Baltimore Lupus Cohort and 8.9% by Urowitz MB, *et al* (1976)¹⁶. However, our study showed Coronary Artery Disease in 7.32% cases.

Arrhythmia was found in the current study of 4.88%

cases comparable to 3-16.0% cases in other studies¹⁴.

In the present study Echocardiographic changes were found in 56.10% cases. Studies by Cujec B, *et al* (1991), Cervera R, *et al* (1992) and Meriem D, *et al* (2018), showed similar observations^{3,18,19}. In one study 16.7% cases of valvular disease were diagnosed clinically although Echocardiography revealed valve involvement in 40.1% patients¹². However, in our study Valvular Heart Disease was diagnosed clinically in 10.98% patients and Echocardiography showed evidence of Valvular Heart Disease in 37.80% patients.

Echocardiographic evidence of pericardial effusion/ Pericarditis was seen in 31.71% cases of our study

Echocardiographic Findings	No of cases (percentage of cases) n=82
Valvular abnormality	31 (37.80%)
Pericardial effusion	26 (31.71%)
Cardiomyopathy	05 (6.09%)
Regional Wall Motion Abnormality	7 (8.54%)
Global Hypokinesia	2 (2.44%)
Pulmonary Arterial Hypertension	4 (4.87%)
Diastolic Dysfunction	20 (24.39%)
Left ventricular Hypertrophy	15 (18.29%)

Echocardiographic findings	Clinically evident	Clinically silent	Total
Positive	30 (36.58%)	16 (19.51%)	46 (56.10%)
Negative	3 (3.66%)	33 (40.24%)	36 (43.90%)
Total	33 (40.24%)	49 (59.75%)	82

P value is < 0.01 (CI 95%)

Lipid	No of cases (Percentage of cases %) [n=82]
Dyslipidaemia	43 (52.44%)
Hypercholesterolaemia	16 (19.51%)
Hypertriglyceridaemia	33 (42.24%)
Raised LDL	12 (14.63%)
Raised VLDL	16 (19.51%)
Decreased HDL	10 (12.19%)

Antibody	No of cases (percentage of cases %) [n=82]
ANA	79 (96.34%)
Anti-ds DNA	39 (47.56%)
Anti Sm	30 (36.58%)
Anti RNP	19 (23.17%)
Anti Ro (SS-A)	9 (11.67%)
Anti La (SS-B)	6 (7.31%)
Anti Histone	12 (14.63%)
Anti nucleosome	27 (31.97%)
Anti Ribosomal-P	26 (31.71%)
Antiphospholipid (APLA)	20 (18.29%)
Direct Coombs test	13 (15.85%)

which was in concordance with results obtained in other studies which showed presence of pericardial effusion in 27%⁵ and 38%²¹ cases.

Diastolic dysfunction was detected in 24.39% cases compared to 16% cases in a study by Cujec B, *et al* (1991)¹⁸.

Cardiomyopathy was found in 6.09% cases. Left Ventricular Hypertrophy was noted in 18.29% cases in Echocardiography which is comparable to 14% obtained in a study by Cujec B, *et al* (1991)¹⁸. Pulmonary Arterial Hypertension was present in 4.8% cases, comparable to other studies showing its presence in 10.1%, 10% and 8.5% cases of SLE^{12,19,20}. In the present study Regional Wall Motion Abnormality was found in 8.54% cases and Global Hypokinesia was present in 2.44% cases compared to 2.8% and 4% patients in other studies^{12,18}.

Hypercholesterolaemia was present in 16 (19.51%) cases and hypertriglyceridaemia was present in 33 (42.24%) cases. Raised VLDL, raised Low-density Lipoprotein (LDL) and decreased High-density Lipoprotein (HDL) were present in 16 (19.51%) cases 12 (14.63%) cases and 10 (12.19%) cases respectively. In a study at a tertiary teaching hospital of Eastern India by Dakua S, *et al* (2017), Hypercholesterolemia was found in 23 (22.7%), Hypertriglyceridemia in 55 (54.4%), raised LDL-C in 24 (23.7%) cases.

ANA positivity was 96% in our study. Malviya AN *et al*, Paul BJ, *et al*, Saigal R, *et al*, Sharma M, *et al* found similar findings in their study. APLA association in SLE was found to be 18.29% cases positive in our study however, a study by Bourre- Tessier J, *et al* (2011) found APLA in 32.7% of cases.

Amongst the patients with Cardiovascular manifestations, 9.09% patients had no disease activity, 39.39% patients had mild disease activity, 21.21% patients had moderate disease activity, 15.15% patients had high disease activity and 15.15% patients had very high disease activity. A study by Mohamed AA, *et al* (2019), reported that there were no significant associations between the Echocardiographic features and the SLEDAI scores, a finding which is consistent with our study²⁰. However, in a study by Cervera R, *et al* (1992), active disease was found in 56%, of whom 67% had Echocardiographic abnormalities³.

CONCLUSION

In the present study, most of the patients presented with fatigue, arthralgia, skin rash, alopecia, photosensitivity. The study revealed pre-ponderance of disease amongst rural population, more specifically

in tribal population. Echocardiographic evidence of cardiovascular disease was found in more than fifty percent of patients whereas only forty percent of the patients were diagnosed clinically. Most common cardiovascular findings detected clinically were Hypertension, Pericardial Effusion, Congestive Cardiac Failure and Valvular Heart Disease. However, Echocardiography Revealed Valvular Abnormality, Pericardial Disease, Cardiomyopathy, Diastolic Dysfunction, Left Ventricular Hypertrophy, Pulmonary Artery Hypertension, Regional Wall Motion Abnormality and Global Hypokinesia in decreasing order respectively. A special observation was made that dilated cardiomyopathy were found in 2 out of 8 male patients and also found in female patients in ethnic groups. Hypertriglyceridemia followed by Hypercholesterolaemia and increased VLDL were the most common lipid abnormalities detected amongst SLE patients. No significant antibody association was seen in patients with Cardiovascular Manifestations unlike Anti ds DNA in Lupus Nephritis. APLA association is seen in Coronary Artery Disease.

Limitations :

Our study had a small sample size and duration of study was short. It was a cross-sectional observational study and patients were not followed up. Hence no definite inference was concluded from this study. A large longitudinal prospective epidemiological study is required to arrive at a definite conclusion.

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Conflict of Interest : None

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Original Article

A Study of Correlation Between Anthropometric Measurements and Carotid Intima Media Thickness in Newly Diagnosed Type 2 Diabetes Mellitus Patients in a Tertiary Care Hospital in Eastern India

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The objective of the study was to find out correlation between Body Mass Index (BMI) and Waist Circumference (WC) with Carotid artery Intima Media Thickness (CIMT) in newly diagnosed Type 2 Diabetes Mellitus (DM) patients (within six month of initiation of antidiabetic drugs). This cross sectional observational study was conducted at Inpatient and Outpatient Department of Medicine and Diabetic Clinic of RG Kar Medical College, Kolkata, West Bengal, India from January, 2018 to June, 2019. Data were collected from 250 newly diagnosed Type 2 DM patients. CIMT was measured by Doppler ultrasound. Mean CIMT of 53.6% overweight and 7.6% obese (as per BMI) participants was 0.90 and 1.26 respectively. Waist Circumference (WC) of 75 out of 140 male participant was >102 cm and WC of 88 out of 110 female participant was >88 cm. Among the participants of increased WC, 53.33% male and 36.66% female had increased CIMT. Higher HbA1C was associated with increased CIMT. This study showed significant correlation between BMI, WC with CIMT in newly diagnosed Type 2 DM patients. Our study demonstrated that Anthropometric Measurements (BMI and WC) are effective, noninvasive tools which can assist in identifying newly diagnosed Type 2 DM patients with increased CIMT predicting increased risk of micro and macro vascular complications.

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Key words : BMI, WC, CIMT, Type 2 DM.

Three major co-morbidities in Type 2 diabetes are Obesity, Dyslipidemia and Hypertension. Other associations are smoking, alcoholism, sedentary lifestyle, chronic kidney disease. In a study by Iglay *et al* (2016) showed that among 1389016 Type 2 DM patients, 97.5% of patients were found to have comorbidity for at least one basic diseases like Obesity, Dyslipidemia and Hypertension¹.

Indians are known to have a unique pattern of Dyslipidemia with Lower HDL cholesterol, increased triglyceride levels and a higher proportion of small dense LDL cholesterol. This type of dyslipidemia with diabetes is more prone to atherogenesis and thereafter cerebrovascular accidents².

Obesity is measured by many standardized

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Editor's Comment :

- CIMT, an ultrasound biomarker of atherosclerosis is considered a marker of subclinical organ damage.
- Diabetic patients exhibit a greater CIMT value. CIMT should be prescribed in all diabetic patients during initial assessment for microvascular complications.

indices. BMI (Body Mass Index) is widely used for measurement and categorization of obesity. Waist Circumference (WC) is used as an obesity (abdominal/central) measure providing more sensitive approach in classification. BMI and WC can be measured with very simple and easily available instruments.

Diabetes and its associated complications such as dyslipidemia, atherosclerosis etc, lead to micro vascular and macro vascular complications. The best way to measure the extent and degree of atherosclerosis is by direct measurement of arterial wall thickness. This can be done by ultrasound guided measurement of thickness of two innermost layers of carotid artery. This is a noninvasive process. Studies have shown that carotid artery wall thickness matches proportionately with intracerebral artery wall conditions.

Thus in this study, a correlation between obesity indexes and carotid artery wall thickness is tried to be established and this correlation can give physicians a perception about the degree of atherosclerosis in

Type 2 diabetes patients by some simple weight, height and Waist Circumference measurements.

MATERIALS AND METHODS

This institution based cross sectional observational study was done in the Inpatient and Outpatient Department of General Medicine, Diabetic Outpatient Department of R.G.Kar Medical College, Kolkata, West Bengal from 1st January, 2018 to 30th June, 2019.

Patients diagnosed as Type 2 diabetes based on undermentioned criteria recommended by American Diabetic Association (ADA) and those having antidiabetic treatment duration of 6 months or less were included in our study. (attending Diabetic Clinic or admitted in Medicine Ward).

ADA Criteria for the Diagnosis of Diabetes:

- HbA1C \geq 6.5% — The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

- FPG \geq 126mg/dL (7mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

- Two-hour plasma glucose \geq 200 mg/dL (11.1 mmol/L) during an OGTT.

The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.*

OR

- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose \geq 200mg/dL (11.1mmol/L).

*In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

Type 1 Diabetes Mellitus, Gestational Diabetes Mellitus, Drug induced hyperglycemia, those with disease of exocrine pancreas, known endocrinopathies like Cushing Syndrome, Acromegaly were excluded from our study.

BMI calculated from their weight (kg) and height (meter) by this formula³.

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

BMI Weight Status (age >20 years) —

Below 18.5	Underweight
18.5 – 24.9	Normal or HealthyWeight
25.0 – 29.9	Overweight (pre-obese)
30.0 and Above	Obese
30.0-34.9	Obesity I
35.0 - 39.9	Obesity II
Above 40	Obesity III (extreme)

Sugar (FBS, PPBS) was measured by Glucose Oxidase Peroxidase method (GOD-POD) HbA1C was measured by immunoturbidimetry method by Transasia EM 360 machine in Biochemistry laboratory of our institution.

Waist Circumference (WC) was measured at a level midway between lowest rib margin and uppermost part of iliac crest (C in the figure) with the tape all around the body in horizontal position (B in the figure). Participants were asked to stand with their feet fairly close together and their weight evenly distributed to each leg (A - umbilical line) (Fig 1).

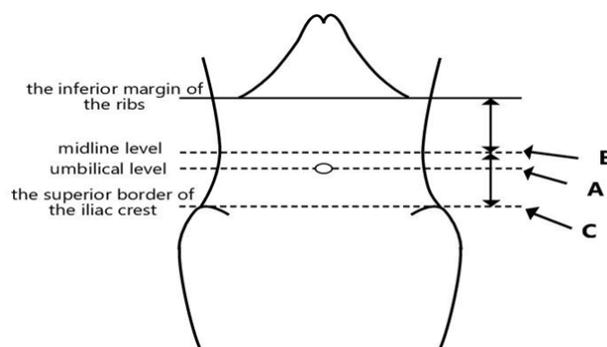


Fig 1 — Measurement of waist circumference

Men and women who have Waist Circumferences greater than 40 inches (102 cm) and 35 inches (88 cm), respectively, are considered to be at increased risk for Cardio Metabolic Disease⁴.

Assessment of WC provides a measure of central fat distribution that cannot be obtained by measuring BMI. Large population studies have found Waist Circumference to be a strong correlate of clinical outcome, particularly diabetes and to be independent of BMI⁵.

CIMT is defined as a double-line pattern visualized by echo 2D on both walls of the Common Carotid Artery (CCA) in a longitudinal view. Two parallel lines (leading edges of two anatomical boundaries) form it: lumen-intima and media-adventitia interfaces (in the Fig 2 distance between yellow and pink line is the IMT).

High-resolution B-mode system (B-mode imaging is preferred over M-mode imaging), equipped with a linear array transducer >7 MHz with minimal

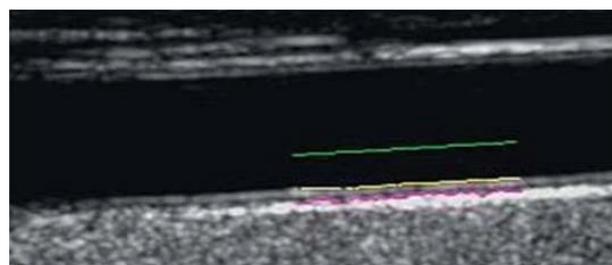


Fig 2 — Ultrasound image of carotid intima media

compression (<10:1) and footprint of at least 3 cm;

In this study maximum cut-off value for normal CIMT is taken as 0.9 mm

With the help of Microsoft word and excel data analysis was done using the statistical Software namely SPSS 11.0 and Systat 8.0. Chi-square and Fisher Exact Test was used to analyze patient demographics and outcome scores. Association between CIMT and BMI was analysed with a multivariable binary logistic regression model.

RESULTS

250 patients participated in the study, 140 were males (56%) and 110 were females (44%). Age of the patients in study population ranged from 20 to 73 years. Mean age 44.36 years. Most of the participants were between 30 to 60 years.

Height of the patients in study population ranged from 1.36 m to 1.92 meters. Mean height 1.63 meters. Weight of the patients in study population ranged from 48Kg to 99 kilograms. Mean weight-70.35 kilograms. 82 were normal BMI (18.5 – 24.9), 142 were preobese (BMI 25 – 29.9) and 26 were obese (BMI >30). Mean BMI in all age group were approximately 26. That means, most subjects were in pre-obese group.

Fasting Blood Sugar of the participants ranged from 134 to 292, Mean FBS 191.45. Postprandial Blood Sugar of the participants ranged from 176 to 430 mg/dl. Mean PPBS 280.7 Among 250 participants, majority (173) were non-smokers, and 77 were smoker and most (200) were non-alcoholics and only 50 were alcoholics.

Out of 250 patients, 117 had HbA1c between 6.5-8%, 96 had HbA1c between 8-10% irrespective of age and sex.

Distribution of Mean HBA1c (%) in BMI Group :

Mean HbA1c were around 8 in all BMI group (Table 1).

Difference of mean HBA1c according to BMI group was not statistically significant.

39.3% cases have CIMT >0.9% having HbA1c level 6.5 – 8% and 42.26% cases have CIMT >0.9% with HbA1c 8-10%. Mean CIMT in normal BMI group was 0.7299 Mean CIMT in over weight group was 0.9003 and Mean CIMT in obese group was 1.2619

Prevalence of higher CIMT (0.9 mm) was found

more among higher HbA1c level & higher BMI group (Table 2).

Waist Circumference was higher in obese and overweight BMI group.

Among the 140 male subjects, 75 had WC>102 cm of which 40(53.33%) had increased CIMT and 88 (among 110 female subjects) had WC>88cm of which 32(36.36%) had increased CIMT. We found that CIMT was positively correlated with Waist Circumference (Table 3) and this correlation was statistically significant.

Among 250 participants, 37.57 % non-smoker and 50% smoker participants had increased CIMT and 37.18% of all non-alcoholic subjects and 58.82% of all alcoholic subjects had increased CIMT.

Table 1 — Distribution of HBA1c(%) among different BMI group

BMI group	Number	Mean	SD	Minimum	Maximum	Media n	p-value
Normal	97	8.1902	1.0982	5.9000	11.0000	8.1000	0.1684
Over weight	134	8.5331	1.4979	5.9000	14.0000	8.1000	
Obese	19	8.5577	1.3063	6.5000	11.0000	8.6000	

Table 2 — Distribution of mean CIMT (mm) among different age group

Age group	Number	Mean	SD	Minimum	Maximum	Media n	p-value
N≤40	97	0.8120	0.2294	0.46	1.50	0.7800	0.0012
41-60	134	0.9312	0.2423	0.38	1.60	0.8850	
61-80	19	0.8926	0.2918	0.54	1.60	0.8700	

Table 3 — Correlation of CIMT in all parameters

	CIMT (mm)	Remarks
AGE(Years) :		
Pearson Correlation Coefficient (r)	0.204**	Positive Correlation
p-value	0.001	Statistically significant.
Number	250	
HEIGHT (meter) :		
Pearson Correlation Coefficient (r)	-0.304**	Negative Correlation
p-value	0.000	Statistically significant.
Number	250	
WEIGHT (Kilograms) :		
Pearson Correlation Coefficient (r)	0.237**	Positive Correlation
p-value	0.000	Statistically significant.
Number	250	
HbA1C (%) :		
Pearson Correlation Coefficient (r)	0.044	Positive Correlation
p-value	0.493	Statistically not significant.
Number	250	
BMI(kg/m2) :		
Pearson Correlation Coefficient (r)	0.635**	Positive Correlation
p-value	0.000	Statistically significant.
Number	250	
Waist Circumference :		
Pearson Correlation Coefficient (r)	0.199**	Positive Correlation
p-value	0.002	Statistically significant.
Number	250	

DISCUSSION

Major cause of death among diabetes population is cardiovascular disease. Major co-morbidities in Type 2 Diabetes Mellitus are hypertension, dyslipidemia, obesity. Associations with smoking, alcoholism, less physical activity may accelerate the progression of micro- and macro-vascular complications of Type 2 Diabetes Mellitus. Major pathological process for these complications is widespread atherosclerotic changes in vessels which start in prediabetic states. By the time, the symptoms of diabetes manifest, the atherosclerotic changes have an extensive progress. This subclinical atherosclerotic changes need to be detected early to reduce the mortality and extend the life span of diabetics by preventing major cardiovascular events.

Many patients are diagnosed late when the osmotic symptoms of hyperglycemia becomes very much prominent. A study in South Korea by Kim CS *et al* suggested that the 2hPG parameter among the various metabolic parameters exerts the greatest influence upon the prevention of carotid IMT progression in type 2 diabetic subjects⁶. The level of 2hPG is an independent risk factor for the progression of carotid IMT in Korean Type 2 Diabetic patients.

The prevalence of obesity in India is varying from rural to urban and State-wise as well due to various factors. The main factors for variation in obesity are geographical condition, life style and dietary pattern. In our study, higher CIMT was found in older subjects of above 40 yrs age (Table 2). A study by Bosevski M *et al* in Macedonia, found that older have a greater probability of detection of increased CIMT.⁷

Diabetic patients who smoke tend to have higher CIMT because smoking is a risk factor for atherosclerosis in diabetics. Alcoholic diabetics also have higher CIMT values as alcoholism is a risk factor for dyslipidemia which in turn causes more atherosclerosis.

When CIMT was plotted against BMI in scattered diagram, CIMT was found to be positively correlated with BMI and this correlation was statistically significant.

Among the different HbA1c ranges, it was found that higher the HbA1c value is associated with increased CIMT. Data from a study conducted in Paris by Tropeano AI *et al* suggest that hyperglycemia is a major independent determinant of CIMT in hypertensive hyperglycemic patients, not only in Type 2 DM patients, but also at the earlier stage of IFG, offsetting the mechanical role of local pulse pressure⁸.

CONCLUSION

For assessment of macro vascular complications of Diabetes CIMT, is a well standardized surrogate marker for assessing cardiovascular risk and it is well accepted as a parameter of subclinical atherosclerosis. CIMT is a strong predictor of future cardiovascular events and is correlated with conventional markers of cardiovascular risk such as age; hypertension and dyslipidemia and also demonstrated that subclinical atherosclerosis increases with increasing degrees of glucose intolerance, abdominal obesity.

This study showed a significant correlation between HbA1c and BMI and Waist Circumference with Carotid Intima Medial Thickness (CIMT). The study also showed a correlation between CIMT and some coexisting modifiable risk factors like smoking, alcoholism, body weight and some non-modifiable risk factors like age, height.

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Original Article

A Pilot Study to Assess the Impact of Zinc Hyper-supplementation on Hospital Stay of COVID-19 Patients — Results of a Prospective Controlled Study

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Introduction: Zinc has been hypothesized to have antiviral benefits and a proposed preventive and therapeutic modality for COVID-19. There are no trials reporting the impact of Zinc supplementation on outcomes of hospitalized COVID-19 patients in India.

Aims : To evaluate the therapeutic benefit of Zinc hyper-supplementation on hospital stay and mortality of hospitalized COVID-19 patients.

Methods : A prospective controlled pilot study was performed in a tertiary care hospital on COVID-19 positive patients. On admission, patients were allocated in two groups- Control group receiving standard of care treatment only and intervention group receiving standard of care + tablet Zinc sulphate 100 mg daily. Primary outcomes studied included duration of stay and mortality between the two groups. All patients were followed up till discharge or death.

Results : One hundred and five patients completed the study, out of which 47 were in Zinc (intervention) group and 58 were in Non-zinc (control) group. Both groups were comparable in terms of age distribution, gender, Body Mass Index (BMI) and prevalence of diabetes and hypertension. 27.6% of cases from control group required Intensive care (ICU) admission which was comparable with 31.9% among intervention group ($p=0.629$). The NEWS-2 severity score was similar in both groups. Mean duration of stay was 8.9 ± 5.1 days in control group which was comparable with 8.6 ± 5.6 days in intervention group ($p=0.771$). Mortality rate was 3.4% in control group and 2.1% in intervention group and the difference was not significant ($p=0.686$).

Conclusion : Though Zinc has been hypothesized to demonstrate therapeutic effect on COVID-19 infections, our pilot study shows no impact of hyper-supplementation of Zinc on duration of stay or mortality. However, larger multi-centric studies are required to understand the role of Zinc in reduction of hospital stay and overall SARS-Cov-2 outcomes in hospitalized patients.

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Key words : Zinc, COVID-19, Hospital stay, Mortality, Prospective study.

As the world continues to be gripped by the Corona virus disease (COVID-19) pandemic, treatment of the disease is still under evolution. The pathogenesis of COVID-19 is not fully understood, but is probably multifactorial, including a systemic exaggerated inflammatory response and associated thromboembolic complications in some cases^{1,2}. Effective vaccination and antivirals are important to dampen the disease burden of the current pandemic. At the same time, it is essential to identify suitable therapeutic agents or supplements to reduce associated morbidity and mortality.

Editor's Comment :

- The benefits of Zinc in reducing hospital stay or mortality in COVID-19 patients is questionable.
- Larger trials are desirable to study the impact of Zinc supplementation in these patients.

One of the hypothesized micronutrient with antiviral effect is Zinc. Zinc is an essential trace element which plays an important role in growth and the maintenance of immune function^{3,4}. Zinc deficiency has been associated with an increased risk of certain infections, including viral infections. Studies have shown that the normal Zinc status of an individual is protective of viral infections and Zinc-deficient individuals are at increased risk of acquiring HIV or Hepatitis C⁴. Few Randomized Trials (RCTs) have evaluated the effect of zinc supplementation on the immunological response. Acevedo-Murillo *et al*⁵ in their study with 103 children (1 month to 5 years of age) with Pneumonia showed a statistically significant clinical improvement (duration of illness, respiratory rate and oxygen saturation) in the Zinc supplemented group compared to placebo.

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They also demonstrated an increase in the cytokine response in Th1 pattern (IL-2 and INF-gamma) only in the Zinc group with Th2 cytokines (IL-4 and IL-10) being elevated or remaining high in both groups. Another randomized trial on oral supplementation of high-dose zinc (150 mg/day) after stem cell transplantation demonstrated an enhanced thymic function and the output of new CD4 T cells⁶. Currently, to the best of our knowledge, there are no prospective trials reporting impact of Zinc supplementation on outcomes of hospitalized COVID-19 patients in India.

In this study, we wish to evaluate our hypothesis that zinc hyper-supplementation in hospitalized COVID-19 patients is likely to reduce hospital stay and mortality.

MATERIALS AND METHODS

A prospective interventional pilot study was performed in a tertiary care hospital. After obtaining Institutional Ethic Committee (IEC) approval, trial was registered with national trial registry. Informed consent was obtained from all patients/relatives to participate in the trial.

Protocol of Trial :

After admission, patients were allocated into either of the two groups as below.

Intervention — Tablet Zinc sulphate 100 mg (Two tablets of Zinconia 50 mg- Zuventus health care)

Duration : 1.5 months (28th July to 17th September, 2020)

Regimen and Dosing :

Group 1 (control group) : Standard of care (Standard of care medications only).

Group 2 (intervention group) : Active Comparator (Zinc sulphate- 100 mg to be taken daily from admission for 1 month) and standard of care treatment.

Study Design : This was a single-centre, prospective study of 105 hospitalised COVID-19 patients, prior to a formal study with proposed sample size of 174 patients in each arm (range from 143-218 depending on assumptions about change in group mean for primary endpoints). We assumed, 80% power ie, beta - 0.02 and α of 0.05; with Standard Deviation (SD)/variance between the group for Mortality rate ie, all-cause mortality (outcome measure) was about 5%; and for the duration of hospital stay was 5 days.

The subjects were assigned either to

- (a) Standard treatment only (control group) or
- (b) Zinc combined with standard treatment (intervention group).

Method of allocation : All patients on admission

were allotted an “in-patient” hospital identification (IP ID) number. Patients with odd numbered IP ID were assigned “group 1” (standard of care) and even numbered IP ID “group 2” (intervention). Due to COVID-19 related limitations of movement in indoor areas and emergency admission of patients in critical condition, alternate allocation based on odd and even IP ID was considered a feasible method.

Eligibility Criteria:

Inclusion criteria :

Subjects were included if they met criteria as outlined below:

- Patients aged 18 years or more
- Patients with diagnosis of COVID-19 on RT-PCR test

Exclusion criteria:

Subjects meeting any of the following criteria were excluded from the study:

- Pregnant or lactating women
- Patients with dementia, learning disability, mental health needs
- Deemed unfit for the study according to the investigator

Follow up: Till discharge from hospital or death

Outcome Measures:

Primary Outcome Measures:

- Duration of hospital stay
- Mortality rate

Secondary Outcome Measures:

- Incidence of ICU admission
- Incidence of pneumonia and respiratory failure
- Incidence of Bilevel positive airway pressure (BIPAP) and mechanical ventilator requirement
- Severity on admission as per National Early Warning Score (NEWS) 2 score
- Blood parameters (CRP)

Statistical analysis: Data was prospectively entered in excel document. Statistician was blinded about the two groups and participants. Categorical data were expressed as percentage (%). Continuous data were presented as mean and Standard Deviation (SD). Statistical analysis was performed using SPSS version 24.0 (IBM Corp NY). Continuous data was analyzed using independent 't' test or Mann-Whitney test depending on normality of distribution. Categorical data was analyzed using Pearson's Chi square test or Fischer's Exact test. A 'p value' of less than 0.05 was considered statistically significant (95% confidence interval). Patients with protocol violation were excluded from analysis.

RESULTS

Out of one hundred and twenty five patients enrolled in the study, 105 (84%) patients were included in analysis. 47 patients were in Zinc (intervention) group and 58 were in Non-Zinc (control) group. Both groups were comparable in terms of age distribution, gender, Body Mass Index (BMI) and prevalence of diabetes and hypertension (Table 1).

Admission Parameters : On admission, 27.6% of cases from control group required Intensive Care Unit (ICU) admission which was comparable with 31.9% among intervention group ($p=0.629$). 79.3% of the cases had fever in control group which was comparable with 74.5% in intervention group and difference was not significant. 58.6% of the cases had cough in control group which was comparable with 63.8% in intervention group. 36.2% of the cases had shortness of breath in control group which was comparable with 42.6% in intervention group. The NEWS-2 severity score was similar in both groups, 3.5 ± 3.1 in control and 3.4 ± 2.9 in intervention group ($p=0.922$). 81% of the cases had O₂ saturation > 95% in control group which was comparable with 78.7% in intervention group. 92.6% of the cases had elevated CRP (> 5) in control group which was comparable with 87.0% in intervention group (Table 2).

ICU patients : Overall, 7(6.7%) patients required ventilator support, 6 (5.7%) required BIPAP support. COVID-19 associated pneumonia was seen in 31 (29.5%) patients and ARDS in 26 (24.8%) patients. No difference was seen in the ventilator requirement, BIPAP support, COVID-19 pneumonia or ARDS in both groups ($p=0.992$) (Table 3).

Outcomes: 3.4% of the cases died in control while 2.1% in intervention group and difference was not significant ($p=0.686$). Mean duration of stay was 8 days (Range 4-28 days) in control group which was

Parameters	Control	Intervention	P value
No of cases	58	47	
Age (Years) :			
Mean \pm SD	56.03 \pm 14.52	54.81 \pm 12.84	0.649
Range	18 – 90 years	26 – 84 years	
BMI :	N = 34	N = 27	
Mean \pm SD	25.83 \pm 4.44	24.33 \pm 2.97	0.121
Range	19.53-42.37kg/m ²	16.88-28.65 kg/m ²	
Gender n (%) :			
Male	43 (74.1)	33 (70.2)	0.655
Female	15 (25.9)	14 (29.8)	
Diabetes n (%)	21 (36.2)	16 (34)	0.817
Hypertension n (%)	28 (48.3)	22 (46.8)	0.881

comparable with 6 days (Range 3-28 days) in intervention group ($p=0.966$) by Mann Whitney test (Table 4).

Further trial on statistically significant sample was discontinued as no significant alteration in primary end points was noticed on interim analysis in this pilot study. Continuation of study was considered futile by the investigators as approved by the Institutional Ethics Committee.

DISCUSSION

Presently, there is no definitive curative therapy for COVID-19. Therefore, the current treatment protocols involve a multimodal approach with antivirals, steroids and anticoagulation therapy⁷. Supplementation with Zinc is increasingly recommended in the management of COVID-19 patients⁸ even though no prospective trial has been undertaken or published on the role of zinc in reducing COVID-19 related morbidity or mortality in hospitalized patients. To our knowledge, this is the first pilot trial comparing outcomes after therapeutic Zinc Hyper supplementation for COVID-19 in hospitalized patients.

In our study, majority of patients were above 50 years of age, belonged to male gender (72.4%) and

Parameters	Control	Intervention	P value
No of cases	58	47	
ICU admission n (%)	16 (27.6%)	15 (31.9%)	0.629
Fever n (%)	46 (79.3%)	35 (74.5%)	0.557
Cough n (%)	34 (58.6%)	30 (63.8%)	0.586
Shortness of breath n (%)	21 (36.2%)	20 (42.6%)	0.507
NEWS-2 score (Mean \pm SD)	3.5 \pm 3.1	3.4 \pm 2.9	0.922
O ₂ saturation >95% n (%)	47 (81%)	37 (78.7%)	0.123
90 – 95%	4 (6.9%)	8 (17%)	
< 90%	7 (12.1%)	2 (4.3%)	
Elevated CRP (>5 mg%)n (%)	50 (92.6%)	40 (87%)	0.349

	Control N (%)	Intervention N (%)
Ventilator	4 (6.9%)	3 (6.4%)
BIPAP	4 (6.9%)	2 (4.2%)
Pneumonia	16 (27.6)	15 (31.9%)
ARDS	14 (24.1)	12 (25.5%)

Parameters	Control	Intervention	P value
No. of cases	58	47	
Mortality	2 (3.4%)	1 (2.1%)	0.686
Duration of stay:			
Median+Interquartile range	8 + 4.75	6 + 4.5	0.966

had a mean BMI of 25 kg/m². Hypertension was reported in 47.6% while type 2 diabetes was present in 35.2% patients. A meta-analysis by Sanyaolu *et al*⁹ on a total of 1786 patients showed 1044 (58.5%) were males with a mean age of 41 years. The most common comorbidities identified in these patients were Hypertension (15.8%), cardiovascular disorders (11.7%) and Diabetes (9.4%).

Fever was the most common reported symptom in 77.1% patients, followed by cough (61%) and shortness of breath (39%). In a Meta-analysis by Yang *et al*¹⁰, the most prevalent clinical was fever (91.3%, 95% CI: 86-97%), followed by cough (67.7%, 95% CI: 59-76%), fatigue (51.0%, 95% CI: 34-68%) and dyspnea (30.4%, 95% CI: 21-40%). In current study, ICU admission was required in 29.5%, while in a meta-analysis by Abate *et al*¹¹ in 25,000 patients it was 32%. A study by Lagier *et al*¹² showed 91.5% patients had a NEWS-2 score of 0-4 and elevated CRP was significantly associated with poor outcomes. In current study, mean NEWS-2 score was 3.5 and an elevated C-reactive protein (CRP > 5 m/dl) was seen in 90% patients.

In the meta-analysis by Abate¹¹, the prevalence of mortality among COVID-19 patients admitted in ICU was 31% (95% CI: 26 to 36). In current study, subgroup analysis showed mortality in ICU patients was 9.7%. In a study by Lagier¹², the duration of stay ranged from 7.3 to 9.2 days while overall mortality was 0.9%. Mean duration of stay in our study was 8.7 days, similar in both groups while overall mortality was seen in 2.9% patients in our study.

Ours is the only prospective study comparing outcomes of supplemental Zinc in COVID-19 hospitalized patients. A similar study by Jothimani *et al*⁷ compared outcomes in patients with Zinc deficiency and normal Serum Zinc Levels. In our study, there was no difference in duration of stay and mortality across the two groups. Similar incidence of ICU admission, COVID-19 pneumonia and ARDS was seen in both groups. In their study⁷, COVID-19 patients (n=47) showed significantly lower Zinc levels when compared to healthy controls (n=45). Further, amongst the COVID-19 patients, 27 (57.4%) were found to be Zinc deficient. These patients were found to have higher rates of overall complications (p=0.009), acute Respiratory Distress Syndrome (18.5% versus 0%, p = 0.06), corticosteroid requirement (p = 0.02), prolonged hospital stay (p = 0.05), and increased mortality (18.5% versus 0%, p = 0.06). The Odds Ratio (OR) of developing complications was 5.54 for zinc deficient COVID-19 patients. A retrospective analysis by Yao *et al*¹³ showed Zinc Sulfate was not

significantly associated with a change in risk of in-hospital mortality (adjusted hazard ratio, 0.66; 95% CI, 0.41 to 1.07; P ¼ .09). A trial by Thomas *et al*¹⁴ in ambulatory (non-hospitalized) patients showed patients who received standard care (without Zinc or Ascorbic Acid supplementation) achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4.4) days compared with 5.5 (3.7) days for the Ascorbic Acid group, 5.9 (4.9) days for the zinc Gluconate Group, and 5.5 (3.4) days for the group receiving both (overall P=0.45). There was no significant difference in outcomes among the treatment groups. A non-randomized trial by Elalfy¹⁵ showed that the combined use of Nitazoxanide, Ribavirin and Ivermectin plus Zinc Supplement effectively cleared the SARS COV2 from the Nasopharynx in a shorter time than symptomatic therapy.

Limitations : Limitations of our study include lack of prior serum Zinc levels, single center with limited sample size as this is a pilot study with short duration of follow up. Also, it was not possible to match the patients on other treatments received due to variability of disease severity.

Conclusion :

Though Zinc has been hypothesized to demonstrate beneficial effect on COVID-19 infections, our pilot study shows no difference of hyper-supplementation of Zinc on duration of stay or mortality. However, larger multi-centric trials are required to understand the role of Zinc in reduction of hospital stay and overall SARS-Cov-2 outcomes in hospitalized patients.

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Review Article

Institutional Guidelines for Safe Surgery in HIV Patients in a Government Medical College

Ramdip Ray¹, Shamita Chatterjee²

Effective Public Health measures have helped to reduce both the number of new HIV infections as well as deaths due to AIDS. However, over 25% of HIV positive individuals need surgical care sometime during their lifespan. Exposure to body fluid carries a risk of HIV transmission from patient to Operation Theatre (OT) personnel during surgery. A coordinated team approach with strict adherence to Institutional Guidelines is required to ensure safety of patient and all OT personnel during surgery on HIV patients.

[J Indian Med Assoc 2021; 119(11): 38-41]

Key words : Surgery in HIV patients, Universal precaution, Institutional guidelines.

HIV infection is an ongoing epidemic in India, even though it is slowing down¹. Still, the prevalence among adults is estimated to be 0.2% in 2017¹, which translates to approximately 21.40 Lakh individuals. Effective Public Health measures have helped to reduce both the number of new HIV infections as well as deaths due to AIDS. This, however, means that there are a significant number of HIV positive individuals who can hope for a reasonable life span not significantly different from normal population. These individuals would therefore need surgical care sometime during their lifespan, both for acute and chronic conditions.

Approximately 25% of HIV / AIDS patients undergo at least one surgery in their lifetime². Patients with HIV infection only, are at a lower risk and less contagious than patients with AIDS. The pre-operative physiological status and the magnitude of the operative procedure are predictors of postoperative outcome. The surgical magnitude remaining the same in both HIV positive and negative patients, it is the pre-operative physiological status that determines the final outcome.

Healthcare workers and Hospital personnel would need to treat such individuals with the care and respect that is guaranteed by law, while taking suitable precautions to protect them as well as other non-HIV persons present in the Hospital at that time.

Blood and body fluids of HIV positive patients must be considered potentially hazardous. Exposure to body fluids does carry a risk of HIV transmission from patient

Editor's Comment :

- Effective Public Health measures have helped to reduce both the number of new HIV infections as well as deaths due to AIDS.
- However, over 25% of HIV positive individuals need surgical care sometime during their lifespan.
- Exposure to body fluid carries a risk of HIV transmission from patient to OT personnel during surgery.
- Coordinated team approach with strict adherence to Institutional Guidelines required to ensure safety of patient and all OT personnel during surgery on HIV patients.

to Operation Theatre (OT) personnel, even though the risk of transmission is extremely low³. The risk increases manifold in case of penetrating needle stick injury with a hollow needle (as compared to a solid needle), deep soft tissue penetration, presence of blood on the needle and prolonged exposure due to presence of blood inside the glove. Risk also increases in case of patients with early viraemia or advanced AIDS.

In routine practice, health care workers are likely to harbor reservations and fears while delivering surgical services to these patients. However, to achieve an uneventful, incident free surgical procedure in HIV positive individuals it should be conducted by a well co-ordinated team in a calm unhurried manner with concern for the patient & for each other, while paying meticulous attention to details.

The principles of safe surgery in HIV are essentially the principles of sound surgical practice, which are applicable to all patients. However, if possible, elective operations in HIV positive patients may be postponed, with the aim of starting the patient on anti-retroviral medication, so that the surgery can be performed on a healthier patient with a lower viral load, a higher CD4 count and Hb level of 10gm/dl or above². This is advantageous for both patient and surgeon.

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The following guidelines are recommended for all Operation Theatre (OT) personnel for protecting both patients and fellow staff.

General Measures :

- Basic hygienic practices with regular hand washing.
- Protection of mucous membrane of eyes, mouth and nose from blood splashes.
- Safe disposal of contaminated waste.

Skin Wounds / Abrasions / Cuts / Dermatitis / Eczema on Surgical Personnel :

- Intact skin and mucous membranes are an important defense against HIV; existing wounds and skin lesions should be covered with waterproof dressing.
- Wounds / skin lesions over the hands / forearms should be covered with sterile dressing.

Proper OT attire (Fig 1) :

- Full face visors or goggles / glasses with sides covered are recommended. Ordinary prescription spectacles may not provide sufficient protection.
- Closed- toe, non-slip boots with leggings or gumboots to be worn; the gown should extend below the upper level of the gumboots / leggings.
- Plastic disposable apron to be worn beneath the gown.
- Disposable gowns with low permeability to blood / body fluids or fluid repellent gowns to be used.
- Double gloving is mandatory as it decreases the chance of hand contamination and needle pricks. Gloves need to be changed if the outer pair gets damaged.
- Customized forearm guard may be made using the upper part of the gloves, after cutting off the fingers.

General OT Practices :

The highest level of theatre discipline should be maintained:

- In experienced personnel should be excluded from the theatre. Training responsibilities in a teaching hospital can be achieved by demonstrating the principles of safe surgery when operating on other low risk patients⁴.
- No extra spectators should be present in the OT.
- Minimum conversation should be ensured inside the OT, ie, no unnecessary instructions, no jokes, no shouting across the table.
- Restricted staff movements in and out of the OT should be ensured when the surgical procedure is on.

- All unnecessary equipment / furniture should be removed from the OT before the operation to reduce the amount of decontamination required after the procedure.

Anaesthesia :

- Anaesthetists should wear complete protective OT gear like the surgeons.
- Protective eyewear is of particular importance during intubation and extubation.
- Anaesthesia machine should be stripped of all but essential equipment before surgery commences.
- Use of heat & moisture exchange filters in the circuit may be considered.
- Disposable circuitry may be used but are by no means essential.

- Screen at the head end should be made mandatory (Fig 2).

- After surgery, components of the circuit may be decontaminated by autoclaving, low temperature steam, or by immersion in 2 % glutaraldehyde (Cidex) for 12 hours.

Handling Sharps :

Penetrating needle-stick injury occurring with a hollow needle has a higher risk of seroconversion (0.36%) as opposed to a solid needle (0%). Hence minimal handling of sharps is preferred.

- Avoid use of sharps whenever possible: consider use of diathermy or scissors instead of scalpels and staplers instead of needles, where appropriate.
- Ensure safe handling and disposal of sharps. Mounting or removal of scalpel blades by hand is not permitted. Use an instrument for this purpose (Fig 3).
- Excess suture lengths should be snipped off from the atraumatic needles before disposal.
- After surgery, all needles / scalpel blades should be placed carefully in a plastic container (the body of a large syringe may suffice!), filled with bleaching solution or 2% Glutaraldehyde before including them among other items meant for safe disposal.

Surgical Technique :

- Pre-op shaving should be avoided: use epilatory creams if necessary.
- Disposable instruments should be used



Fig 1 — Attire of OT personnel during surgery of HIV positive patients

wherever possible / available.

- Incisions need to be adequate and well planned (eg, midline incisions bleed less).

- Ensure neutral area transfer of sharps using a kidney dish. No direct hand to hand transfer of scalpel / needles should be done (Fig 4).

- Only one hand should move at a time within the operative field, while all others should remain passive.

- Suction bottles should be half filled with 2% Glutaraldehyde before surgery.

- Stiff sutures like Polypropylene should be avoided. The needle, at times, tends to stand up and swing dangerously in mid-air towards the end of a continuous suture.

- Skin staplers should be used whenever possible.

- While unnecessary and excess instruments should not be laid out on the instrument trolley, avoid using fewer instruments than usual because of sterilization concerns: a spare haemostat may not be available when an artery spurts!

- Closed drainage is preferred over an open drain.

Blood Spills :

- If heavy blood loss is expected, OT tables and attachments should be covered with plastic sheets.

- In case of blood spills, a mop soaked in a bleaching solution with available chlorine of 10,000 ppm, should be placed over the area before cleaning the spill. It is useless to sprinkle dry bleaching powder over the blood spill.

Laparoscopy :

- Whenever possible minimally invasive, endoscopic surgical techniques should be employed, this reduces the risk of contamination by blood and body fluids.

- Minimal access surgery is safe in patients with HIV⁵. There is no evidence that HIV is transmitted by aerosols during Laparoscopy. However, instead of 'letting out' the pneumoperitoneum by withdrawing the ports suddenly (blood-mixed carbon dioxide comes out at a force!), the insufflator should be stopped and the pneumoperitoneum sucked out before withdrawing the ports gently.

After Surgery :

- It is not necessary to place high risk patients at the end of the operating list, though before the next



Fig 2 — Screen at the head end



Fig 3 — Mounting or removal of scalpel blades

operation the theatre floor should be disinfected with bleaching powder solution.

- A wound dressing with an impervious outer covering should be used so that there is no seepage of any wound exudate.

- Skin should be cleaned to ensure that no blood remains on the patient's body after completion of surgery.

- It should be ensured that the patient is wearing a clean gown when being sent back to ward after surgery.



Fig 4 — Neutral area transfer of sharps using a kidney dish

- After the operation all drapes / gowns / gloves / disposable instruments should be sealed in a plastic bag. Though disposable drapes and gowns are preferred, if reusable ones are used, they should be labeled as 'infected linen' and send to the laundry.

- Specimens and its accompanying forms should be labeled as 'Biohazard'.

- Instruments should be sent to Central Sterile Supply Department (CSSD) with a 'Biohazard' label. All reusable instruments should be immersed (after dismantling, if required) in bleaching solution or 2% Glutaraldehyde for 1 hour before being taken up for cleaning / washing / sterilization. Hollow instruments / tubes / endoscopes / trocars are perhaps best kept immersed for 12 hours, in the absence of concrete guidelines about sterilisation of such instruments.

After an Injury / Mucosal Splash :

- The surgeon should stop operating as soon as the operating conditions allows, remove gloves and wash the area with soap & water or surgical detergent scrub.

- The wound should be encouraged to bleed, cleansed with alcohol-based wipes and covered with a sterile dressing before re-gloving and completing the operation (unless someone else can take over).

- For mucous membrane exposure, the area should be copiously irrigated with water.

- Full Postexposure Prophylaxis (PEP) protocol should be commenced ideally within 2 hours and definitely within 72 hours of the injury / exposure.

- Counseling and psychological support of the exposed personnel.

- Exposure should be documented and reported to the HIV/AIDS clinic mandatorily on the same / next day.

- Baseline HIV antibody should be tested and PEP continued for 28 days.

- Follow-up HIV antibody testing has to be done at 6 weeks, 12 weeks and 6 months.

CONCLUSION

Surgery for patients with HIV/ AIDS should not be a panacea for the treating surgeon and the entire surgical team. A coordinated team approach is needed with proper pre-operative preparation to ensure a systematic, step wise approach which is duly practiced even during operating on non-HIV / AIDS individuals so that individual team members are aware and are accustomed to their roles during such situations. Training of all involved personnel is also necessary so that the correct response is made in a professional manner in the event of an adverse event / incident. This would ensure honoring the commitment of the Medical profession towards such individuals and thus maintain the spirit of the enacted law as well.

Disclaimer : These guidelines are developed partly from a review of published literature and partly as a result of the 'felt needs' of surgical personnel involved in operations on HIV positive patients. However, these guidelines are still in the process of being validated and are no substitute for the judgement / discretion of the individual doctor / surgeon.

Conflict of interest : None

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Review Article

Point of View — Diabetes & Cardiovascular Disease in Rural India : A Hidden Link ?

Krishnan Swaminathan¹, A Muruganathan²

There is a worrying increase in Diabetes and Cardiovascular Diseases in Rural India. Most of the research in India is focussed on diet, lifestyle and traditional risk factors. Anecdotally, we see a lot of farmers from rural areas with minimal history of traditional risk factors but Florid Diabetes and Vascular Disease. We believe that Agrochemicals and Diabetes is a “hidden link” that has been largely unexplored in the Indian subcontinent. Studies focussed on environmental endocrine disruptors, especially pesticides and heavy metals is the need of the hour in rural Indian populations. Such studies will help in solidifying a causative link, improve rural healthcare, inform Governmental Regulatory Agencies on safer policies and reduce rural disease burden.

[J Indian Med Assoc 2021; 119(11): 42-3]

Key words : Diabetes, Cardiovascular Disease.

South Asia, particularly India, home to around 18% of the World's Population, is currently in the midst of an epidemiological transition from infectious and nutritional illness to Non Communicable Disease (NCDs), especially Cardiovascular Disease, predominantly driven by a cluster of “traditional risk factors” like Diabetes, Pre-diabetes, Obesity, Diet & Lifestyle, hypertension, hyperlipidaemia and atherosclerosis. Individually, each of the above risk factors has huge healthcare, economical and societal implications. Collectively, this “Axis of evil” is a disaster in the making for India and a “ticking time bomb” that will wreak the Nation's Health.

An important driver in the huge explosion of Diabetes and Hypertension in India has been the changes in diet, lifestyle and physical activity. In fact, poor physical activity and unhealthy diets have emerged as the two most important modifiable risk factors for prevention of Diabetes and Cardiovascular disease¹. In one of the largest scientific study in India looking at physical activity in different regions, nearly half of the population in four different regions of India were inactive. This translates to 392 million inactive individuals in India! Even among those who spent time in recreational physical activity, the overall duration of moderate to vigorous physical activity was less than twenty minutes per day². Coupled with the choice of unhealthy foods, this sets the platform for an ‘Obesogenic environment’ that has huge implications for the burden of Non-communicable Diseases in India. Indians have a propensity to have a higher content of visceral fat for a similar Body Mass Index (BMI),

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Editor's Comment :

- The epidemiological transition from Infectious to Non-Infectious Diseases like Diabetes and its complication has brought into focus the Non-traditional Factors involved in evolution of Diabetes.
- It is speculated that chronic exposure to pesticides in low dose, in the form of unwashed fruits and vegetables may lead to development of Insulin resistance and Diabetes gradually.
- Further studies in this matter may help in confirming this speculation.

compared to Caucasians, famously termed the “Y-Y Paradox”³. There is good evidence linking visceral fat to increased risks of Diabetes and Pre-diabetes. Therefore, even a minimal increase in weight can increase the visceral fat, which in turn translates to a higher risk of Diabetes and Cardiovascular diseases.

The concern for all healthcare professionals and policy makers is the fact that the transition in both the risk factors and Cardiovascular Diseases in India has occurred over a relatively short period of time⁴. To compound this, India is a “Nation within a Nation”, where many states have populations close to that of countries in Europe! Therefore, there will be huge regional variations in diseases and risk factors that will have a bearing on how scanty resources can be utilised to optimise healthcare. Our concern is primarily centred towards rural Indian population where the triple burden of lack of awareness, healthcare costs and poor healthcare facilities add significantly to morbidity and mortality from non-communicable diseases. The progression of this NCD epidemic, especially in rural areas, is characterised by a multitude of factors including rapid urbanisation, reversal of socioeconomic gradients, fast food culture, less intake of fruits and vegetables, tobacco and alcohol use/ abuse, less access to healthcare in the poorer socioeconomic strata of the society and much more. Efforts to understand the Pathophysiology of this transition has been traditionally

focussed on the above factors. However, there is growing body of evidence for the role of non-traditional risk factors, especially Pesticides, in the development of Diabetes, Pre-diabetes, Hypertension, atherosclerosis and cardiovascular disease.

Pesticides & Diabetes ?

Our interest in pesticides and diabetes was sparked by case of a fifteen-year-old girl with pesticide poisoning masquerading as Diabetic Ketoacidosis, a major Medical Emergency, Causing great uncertainty in treatment⁵. There have been several other case reports of organophosphorus poisoning presenting as Diabetic Ketoacidosis^{6,7}. In one of the cases, a young boy had apparently taken unwashed, pesticide sprayed tomatoes from a field and presented with diabetic ketoacidosis. His clinical condition deteriorated even though his metabolic parameters improved and the diagnosis was finally made with very low cholinesterase levels. Once the child (and our patient) received Atropine and Pralidoxime therapy, which are anti-dotes to organophosphates, he made a dramatic recovery and had no diabetes in a four week follow up. Therefore, OP poisoning may occasionally overwhelm Glucose Homeostatic Pathways in selected patients and present as Diabetic Ketoacidosis with potential for erroneous treatment. If Organophosphates in acute poisoning can cause severe hyperglycaemia, is it possible that long term exposure to pesticides in our rice, fruits and vegetables are a "cog in the wheel" for the Huge Diabetes Epidemic we see in our populations? Is it possible that farmers and rural subjects exposed to pesticide sprays and mixtures over a long period of time become Diabetogenic? This is a pertinent question as pesticide use is not only well entrenched but has dramatically increased with an estimated 5.2 billion pounds Worldwide use in 2006-7. There are different types of pesticides available but the ones that are widely used include the Organophosphates (OP), Organochlorines (OC) and Carbamate (CB). Newer pesticides including Nicotinoid pesticides and insect growth regulators are also finding their way into the market. OP's can be absorbed through intact skin and also from the gastro-intestinal tract after ingestion of contaminated food⁸. The vapours are also capable of penetrating the Skin, Cornea and the Respiratory Epithelium. Apart from Neuro and Cardio Toxicity, Organophosphates and Organochlorines seem to affect multiple pathways that affect Glucose Homeostasis, that collectively contribute to Hyperglycaemia⁹. This includes effects on Glycogenesis, Glycogenolysis, Glycolysis, Gluconeogenesis, Insulin expression, stress induced activation of Hypothalamic-Pituitary Adrenal axis (HPA), Autonomic Nervous System, Oxidative stress, Inhibition of Blood Paraoxonase Activity, Pancreatic inflammation, Adrenal

Gland Stimulation leading to Hyper Secretion of Adrenaline and alterations in metabolism of liver enzymes¹⁰.

Clinical Implications :

Pesticide use is highly settled in the World today, not only in agriculture but also in the urban settings (homes, workplace, outdoors) for termite and mosquito control. Not to be forgotten is the amount of low dose chronic exposure to pesticides in unwashed fruits and vegetables that we consume every day. A number of human studies and animal studies clearly suggest a signal in terms of acute and chronic pesticide exposure with the development of Insulin Resistance and Diabetes. Considering the Epidemic of Diabetes, it is always worthwhile to think about non-traditional factors in the Pathophysiology of Diabetes, especially in Rural India. Clearly the ubiquitous use of pesticides is an attractive "Diabetogenic Link". Studies focussed on those who are occupationally exposed to pesticides, especially farmers, may prove vital in clarifying a causative link. Such studies may play an important role in health promotion, preventive care, a shift in thought as well as Action by governmental regulatory agencies and importantly provoke new research so than products that are more "Metabolic Friendly" become easily available.

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Review Article

Update on Immunological aspects of COVID-19 Infection

Nallasivan Subramanian¹

COVID-19 Pandemic has shaken the world since Jan 2020 and countries are struggling now with second wave peaking in eastern nations while vaccine drive is going on in the western world. Exposure to the SARS-CoV-2 causes multisystem disease and not limited to lungs and airways. After initial viral replication triggers the cytokine storm, the inflammatory cascade sets in and causes multiorgan disease, however lungs bore the brunt of the attack still. Patients develop a dysfunctional immune response with activated macrophages resulting in high levels of plasma cytokines including IL-6, TNF- α , IL-8, IL-10 and IL-1RA and altered coagulation pathways. Though the 2 week period of viral infection may settle in most patients without much systemic upset, there are patients who have post covid sequelae and health consequences. Serum CRP, LDH, Ddimer and IL-6 levels have been found to be reasonable biomarkers in patients with COVID-19 infection and many studies have shown direct correlation with clinical profile. Further continued research on the immunological aspects will help elucidate the reasons for widespread disease in spite of efforts by WHO and all nations. Mutant strains, drug availability and the medical expenditure will be the foremost in managing this pandemic. This article gives a summary of immunological aspects of COVID-19 and current understanding of this viral infection.

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Key words : COVID-19, Cytokine storm, SARS Cov2, Mutant, Thrombosis, Lung injury.

COVID-19 pandemic has shaken the World resulting in huge loss to the mankind in 2020 and now spreading fast as second wave although countries have been taking steps to control this pandemic. According to AIIMS (All India Institute of Medical Sciences) Chief on 1st April 2021, COVID second wave has started in India exactly like what UK experienced in Dec 2020 and has the propensity to affect adolescents.” COVID Vaccination efforts have been ramped up with more sustained campaigning across the health sector, media and the public.

Exposure to the SARS-CoV-2 causes multisystem disease and not limited to lungs and airways. Currently patients manifest with fever, fatigue, diarrhea, vomiting, breathlessness and stroke. COVID-19 is spreading with mutant variants and vaccination is also being undertaken across the World. Postcovid, people suffer with multitude of symptoms including arthralgia, myalgia, deep vein thrombosis and breathlessness. In this article we report the concise information on immunological aspects of COVID-19 infection.

Pathophysiology :

Once a patient becomes infected with SARS-CoV-2, adaptive immunity develops and serum IGA and IGM

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Editor's Comment :

- COVID-19 infection has mutant strains and vaccination strategies should focus on the immunological changes while producing the newer vaccines across the different countries.
- SARS-CoV-mediated disease is largely immune driven with complement activation resulting in SIRS- Systemic Inflammatory Response Syndrome and also thrombogenic vasculopathy.
- Social distancing and universal masks would help in reducing the transmission of this covid virus which may be still active over the next few years.

antibodies develop by 5 to 7 days and IgG by 10 days. Tcell activation results in specific CD4 cells and CD8 which stay in circulation. Grifoni et al have demonstrated that in patients recovering from COVID-19, specific memory CD4 T cells were seen in 100% and CD8 T cells in 70% of patients¹.

Once virus enters the humans through respiratory epithelium, viral contents are released inside the host cells, mRNA replication occurs and protease cleavage happens resulting in the release of cytokines. Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2 which are abundant in lung, heart and kidney. Although severe COVID-19 is characterized by high-viral load and dysregulated immune system, antibody-dependent cytokines like- IL-4, IL-5, do not contribute to severity of acute infection. Understanding the important features of B cell and T cell mediated immunity play pivotal role in the management of this infection and

the ensuing inflammation².

The high level of anti-SARS-CoV-2 IgG and IgA titers to the spike protein correlates well in patients with CD4+ T-cell responses and the level of IgG1 and IgG3 Enzyme-Linked Immunosorbent Assay (ELISA) titres correlates well with viral neutralization³.

Immunological aspects :

SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells (precursor for type I cells).

Monocytes/macrophages play a crucial role in anti-viral responses by linking innate and adaptive immunity. Peripheral activation and accumulation of activated pro-inflammatory monocytes/macrophages within lungs has become one hallmark of symptomatic SARS-CoV-2 infection.

In severe cases, fatality is due to severe lung injury characteristic of Acute Respiratory Distress Syndrome (ARDS). This pathology is characterized by intense, rapid stimulation of the immune response that triggers activation of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathways and release of its products including the proinflammatory cytokines IL-6 and IL-1 β ⁴.

What is NLRP3 Pathway ?

The NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome consists of a sensor (NLRP3), an adaptor (ASC; also known as PYCARD), and an effector (caspase 1). NLRP3 contains an amino-terminal pyrin domain (PYD), a central NACHT domain (domain present in NAIP, CIITA, HET-E, and TP1) and a carboxy-terminal leucine-rich repeat domain (LRR domain). The NACHT domain mediates ATPase function that is vital for NLRP3 self-association and function and the LRR domains auto regulate through folding back onto the NACHT domain. ASC has two protein binding domains, an amino-terminal PYD and a carboxy-terminal caspase recruitment domain (CARD). NLRP3 can oligomerize between NACHT domains upon stimulation which leads to ASC recruitment through PYD-PYD interactions⁵.

Cytokine Storm :

In SARS-CoV-2 infection, a cytokine storm occurs resulting in elevated inflammatory biomarkers including C-reactive protein, D-dimer, and ferritin⁶. Patients experience altered immune response with activated macrophages resulting in high levels of cytokines including IL-6 and TNF- α ⁷. Patients develop acute lung injury, acute respiratory distress syndrome, systemic

inflammatory response syndrome (SIRS), Macrophage activation syndrome and coagulopathy⁸. Patients affected with SAR Cov2 who had biopsy studies showed infiltration in pulmonary capillaries by neutrophils and extravasation into the alveolar space⁹. Neutrophil Extracellular Traps (NETs) can be released. Although this is a way to ensnare pathogens, NET formation is linked to pulmonary diseases, particularly acute respiratory distress syndrome.

While eosinophils have protective effects in different viral infections, a significant amount of COVID-19 patients present with eosinopenia, although it is not reported in all cohorts. The pathophysiological mechanism of eosinopenia in COVID-19 patients may be related to increased apoptosis, and decreased eosinophil egression from the bone marrow¹⁰.

Complement and SARS-CoV-2 :

The complement system is involved in both coagulation and inflammatory pathways. Histologic and immunohistochemical analysis of lung and skin have been conducted in patients with COVID-19-induced ARDS. The specific lung findings for ARDS were accompanied with deposits of C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL) - associated serine protease (MASP) 2, in the microvessels¹¹.

Skin biopsies showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of complements C5b-9 and C4d. Severe COVID-19 patients develop catastrophic microvascular injury syndrome with complement activation and coagulopathy. Therefore SARS-CoV-mediated disease is largely immune driven with complement activation resulting in SIRS- Systemic Inflammatory Response Syndrome.

Clinical Features :

The median incubation period from initial infection to symptom onset is 5 days with the majority (97.5%) developing symptoms within 11.5 days. Common symptoms of infection include fever (72%), Shortness of breath (71%), Cough (69%), Tiredness (46%), coughing up sputum (26%), Aching muscles or joints (21%), Headache (13%) and Sore throat (10%)¹² (Table 1). Other symptoms reported include loss of Taste (50%) and Smell (66%). Patients with mild disease recover in 7 days. In more severe cases, patients may continue to cough with malaise for 2 to 4 weeks. In severe infection, breathlessness becomes marked 7–10 days after symptom onset as the infection causes inflammation in the lungs that impairs oxygen exchange. Vascular involvement like deep vein

Table 1 — Showing manifestations of acute SARS Cov 2 infection

Clinical features	Percentage
Fever	72%
Shortness of breath, cough	70%
Fatigue	46%
Loss of taste	50%
Loss of smell	66%
Myalgia	21%
Headache and sorethroat	13%

thrombosis and mesenteric ischemia have been reported during the second week of infection. Those who were discharged may need home oxygen support while convalescing from lung injury.

Systemic Manifestations following COVID-19 Infection :

While COVID-19 was initially considered a respiratory illness, it is now evident that inflammation and fibrosis shall affect multiple organs including lung, heart, kidneys, liver, and gastrointestinal tract and even cause stroke and vasculitis. The extent of disease partly reflects the distribution of the cellular receptor for SARS-CoV-2, Angiotensin-Converting Enzyme 2 (ACE-2), but also the indirect effects of inflammatory cytokines with complement activation leading to thrombotic complications, pulmonary embolism and stroke. Ningombom and colleagues have shown that countries with higher prevalence of exposed obese individuals (with higher ACE2 levels) experienced the highest number of mortalities¹³.

Long Term Health Issues of COVID-19 Infection :

Avila et al have reported that 31% of ICU patients with Covid 19 have developed thrombotic complications including acute cerebrovascular events, impaired consciousness and muscle injury. These complications were seen in patients with severe respiratory impairment, affecting up to 45% of such patients¹⁴. The cardiac manifestations included myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thrombosis. Few patients after recovery from severe infection present with features of chronic fatigue syndrome.

Can Patients Get Reinfection ?

Patients who had contracted COVID-19 and treated, also have susceptibility to reinfection as the immune response is not sustained for long. Researchers have demonstrated a decline in IgG neutralizing antibodies to SARS-CoV-2 in convalescence, raising a possibility to repeat infection. Antibody levels always decline too after the acute illness, because most of the plasmablasts, the “effector” response of B cells,

induced during the first week after infection are short-lived. A similar response is seen with the effector CD8+ T-cell response¹⁵. Patients are now manifesting with recurrent infection even though they were treated for COVID-19 and then got vaccinated.

Mutant Strains :

Various strains of the novel corona virus have been spreading in different countries and according to WHO they have been labelled as per Greek letters. Alpha strain (B.1.1.7 – UK), Beta (B.1.351- South Africa), Gamma (P.1-US), Delta (B.1.617.2- India) have been named and two more- Epsilon and Iota have been identified in the United States. Scientists are wondering if the mass vaccination will help control this mutant virus of SARS Cov 2 across the world.

Conclusions :

World is living on the edge with 18 months of human life curtailed by this pandemic with economical and social impact and 2021 will most likely be swamped by more aggressive disease. Further continued research on the immunological aspects will help elucidate the reasons for widespread disease in spite of efforts by WHO and all nations. Mutant strains, drug availability and the medical expenditure will be the foremost in managing this pandemic. The pandemic demands action on multiple strategies, from prevention to testing to treatment. Still lot of unknowns in this covid 19 infections and further research to develop virus neutralising antibodies may help to contain this pandemic to a reasonable extent.

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Review Article

Circumcision : Myths and Facts

Amit Kumar¹, Bindey Kumar², Rashi Rashi³, Ram Jeewan⁴, Amit Kumar Sinha⁵, Md Mokarram Ali¹

Since time immemorial one of the commonest surgery performed in the History of Mankind is Circumcision. The medical indications with sociocultural overlay surrounds it as a mysterious entity. This age old practice has been re-evaluated in the light of evidence regarding its relevance and usefulness in today's practice. Religious and medical indications has been reviewed in this article and Common Myths have been busted in light of emerging evidences.

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Key words : Circumcision, Phimosis, Sexually transmitted diseases, Urinary tract infection.

Circumcision means removal of penile foreskin. The evidence of Circumcision being done was seen in Ancient Semitic people like Egyptians & Jews. In the wall painting of Egyptians thumb around 2300 BC, there have been ritual of Circumcision among Judaism & Islam, citing improve penile hygiene & lower risk of infection. But, Buddhism & Hinduism along with European had a neutral take over it¹.

Phimosis, paraphimosis and balanoposthitis along with Balanitis Xerotica Obliterans (BXO) forms common etiological factors for Circumcision². The prevention of recurrent Urinary Tract Infection (UTI), HIV infection and Invasive Penile Cancer are other indications for circumcision³.

In Jews Community Circumcision is performed on 8th day of life. In the Muslim wide variability of age is seen regarding Circumcision ritual⁴. Sexual attributes of prepuce are given to increased number Meissner's corpuscles, secreting pheromones and stimulation of partner's genitalia giving her erotic pleasure. The protective function of foreskin have been related with prevention against injury, against UTI, extremes of temperature and by secreting lysosome making bacteriostatic film over the glans⁵. There are opponents of religious Circumcision and they emphasized the function of foreskin in many protective and sexual roles. They consider circumcision unnecessary, unscientific and disrespectful as it mutilates the body image & integrity. Other arguments against the Circumcision are the complications like meatal stenosis, poor breast

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Editor's Comment :

- Proper phallus examination to rule out congenital diseases before undertaking circumcision.
- Proper pre-operative evaluation to rule out bleeding disorder.
- Consideration of topical steroid as non-surgical management.
- A proper written and informed consent regarding complications of circumcision.
- Usage of device is a must only if one is well versed with it.

feeding and poor cognitive development⁵.

We shall analyze the data in the backdrop of claims of benefit and counter claims about harm regarding status of Circumcision mainly based on medical grounds.

Circumcision in HIV :

Evidences are furnished for beneficial role of Circumcision in population at risk of HIV (Human Immunodeficiency Virus). The association of chemokine receptors CCR-5 and HIV colonization on these receptors are linked. Also foreskin contains Langerhan cells, CD4 T cells and macrophages which are common target cells for HIV⁶.

Urinary Tract Infection (UTI) and Circumcision :

It has been seen ten times lesser risk of UTI in circumcised male infant than uncircumcised. A systematic review on reduction of risk of UTI shows risk reduction in the odds of 90%⁷. Studies also reveal that incidence of UTI in boys are far less than the number of complications of Circumcision. Hence, routine Circumcision is not recommended for prevention of UTI. The undisputed roles of Circumcision in various studies have been assigned to cases of recurrent UTI.

Sexually Transmitted Disease and Circumcision :

Common sexually transmitted diseases like HPV (Human Papilloma Viruses) Genital Herpes, Chancroid, Syphilis are prevented by male

Circumcision. There are many studies which cite little support or altogether refute these findings. Male Circumcision may act like a global vaccine to reduce the burden of infections transmitted by sexual contacts⁸.

Cancers and Circumcision :

Invasive Penile Cancer and Prostate Cancer are being prevented if Circumcision is done. Increased susceptibility to penile carcinoma among uncircumcised men may be mediated by Human Papilloma Viruses (HPV). The cervical carcinoma among female partner is also reduced as in circumcised men.

In a systematic review by Larke, *et al* concluded that men circumcised in childhood /adolescences are less prone to develop invasive penile cancers. The explanations postulated that removal of foreskin leads to depletion of smegma which causes repeated inflammation leading to cancerous changes⁹.

Arguments against Circumcision :

Common arguments proposed in opposing non therapeutic male Circumcision of minors for urinary Tract Infection in infancy is unnecessary and of little consequences and can be easily managed with antimicrobials both therapeutically and prophylactically.

The physical harm along with complications in the form of Meatal Stenosis, Glans Amputation, Urethrocuteaneous Fistula and Keratinization of Glans, make circumcision not a good option. In some studies, the reduction in sexual function in the form of decreased sexual gratification has been reported. The risk of HIV or sexually transmitted disease in hetrosexual intercourse has been challenged and simple barrier methods are advocated. The benefit of carcinoma is also contested in the light of rarity of penile carcinoma cases. The view of Human Rights Advocacy Group wants to hold Circumcision until boy is old enough to decide for himself¹⁰.

Indications of Circumcision :

Absolute indications for Circumcision includes Phimosis, paraphimosis, recurrent balanoposthitis and Balanitis Xerotica Obliterans (BXO). Absolute contraindications of Circumcision includes many congenital conditions like Hypospadias, Chordee, Webbed Penis. These patients should be evaluated carefully because redundant foreskin may be required for Penile Reconstruction, in Future Reconstructive Surgeries¹¹.

Age of Circumcision :

The Neonatal Period is optimal & ideal age for Ritual Circumcision. Circumcision in infancy carries lower costs & lower risk of complications¹².

Operative Interventions :

The goals of Circumcision are excision of foreskin along with inner prepuce skin, prevention of glans injury, proper hemostasis and cosmetically good looking phallus.

There are various methods for Circumcision which are broadly categorized into three types. These are free hand excision, slitting the prepuce dorsally and various devices used as shield & clamp. The Gomco clamp and Plastibell clamp are shielded devices used for Circumcision. The Mogen clamp is a non-shield device, so there is more chance of glans injury¹³.

A meta-analysis was done in 2017 to assess the safety and efficacy of disposable Circumcision suture devices in the management of redundant prepuce and phimosis. In this study, it was found that Circumcision suture devices were better and safer than conventional Circumcision¹⁴. Yu Fan *et al* in 2016 to evaluate the safety and efficacy of insitu devices and circular disposable devices and concluded that insitu devices were found to have less intraoperative blood loss, less operative time and better wound healing¹⁵.

A meta-analysis was done to see the effect of three Circumcision techniques (Conventional circumcision, Shang Rings & Disposable Circumcision suture devices) and concluded that disposable Circumcision suture device had advantages over other procedures like shorter operative time, better penile cosmesis, fewer complications and shorter wound healing time¹⁶.

A meta-analysis was also done to evaluate the efficacy of tissue glue in Circumcision and found that tissue glue has reduced operation time, postoperative bleeding, hematoma, postoperative pain and also gives better cosmetic appearance¹⁷.

Chemical Circumcision :

Various literatures suggest that phimosis is over diagnosed & over treated. Sometime prepuce adhesion is mis-diagnosed as true phimosis and Circumcision performed¹⁸.

It is usually seen that problem with foreskin retraction at age of 3 years were 10% and at age of 16 years were 1%, 0.5% Betamethasone is commonly used for chemical circumcision. Due to anti-inflammatory effect & skin suppling effect Betamethasone is used in phimosis¹⁹.

Nicola zanuperi *et al* in his study concluded that early treatment with topical steroid shows much better result with high response rate between 4-8 years of

age. They analyzed 12 studies that included 1395 boys aged between 18 days to 17 years and it was found that topical steroid may be a safe alternative to treat phimosis in boys before undergoing surgical treatment²⁰.

Complications of Circumcision :

Approx one in three men are circumcised globally. Neonates and infants have fewer complications than older children. Overall complication rate was 2%-10%. Bleeding and infection are most common complications²¹.

Special Conditions :

In Circumcision of Hemophilic patients bleeding and hematoma are the most common complication. If patient was diagnosed prior to surgery and appropriate preventing measures were taken then the risk of bleeding was insignificant. On the other hand if it was discovered postoperatively the risk of bleeding significantly increased to 30%. Hematoma formation was seen ranging from 0.2 to 43% in hemophilic patient²².

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Case Report

Extrapulmonary Tuberculosis Complicated by Focal Segmental Glomerulosclerosis — A Rare Association

Biva Bhakat¹, Angan Karmakar², Sukdeb Das³

Focal Segmental Glomerulosclerosis (FSGS) usually presents with reduced glomerular filtration rate, heavy proteinuria and has unfavourable prognosis. Numerous associations with FSGS are found. We encountered a case of FSGS associated with Tubercular Lymphadenopathy presenting with proteinuria, anasarca, nephropathy. 40-year-old female patient presented with Pyrexia of Unknown Origin (PUO) for 4 months and anasarca for 2 months, associated with generalised Lymphadenopathy. Routine evaluation showed Microcytic, Hypochromic anaemia, Raised ESR, Hypoalbuminemia, impaired Renal Function Test and Nephrotic Range Proteinuria. Malarial Parasite (MP), Microarray pooled DNA analyzer (MPDA), Human Immunodeficiency Virus (HIV) 1&2, HBsAg, anti HCV Ab, Antinuclear Antibody (ANA), ANA profile was negative. Excision Biopsy from supraclavicular lymph node showed well-formed granuloma with wide areas of caseous necrosis ie, Granulomatous Lymphadenitis. Renal Biopsy showed Focal Global Glomerulosclerosis. Treatment included anti-Tuberculosis drugs which resulted in a partial improvement in renal function and proteinuria and regression of lymphadenopathy. Tuberculosis can cause renal disease in a number of ways. To the best of our knowledge, very few cases in which tuberculosis was associated with different forms of Glomerulonephritis have been reported in the literature, however, association of FSGS with Tuberculosis is extremely rare, making our case truly atypical.

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Key words : Extra Pulmonary Tuberculosis, Granulomatous Lymphadenitis, Nephrotic Syndrome, Focal Segmental Glomerulosclerosis.

FSGS is responsible for 35% of cases of Nephrotic Syndrome in adults. Though viral infections [Parvovirus, HIV, Hepatitis B, Cytomegalovirus (CMV)] are commonly associated with FSGS, association of bacterial infection with FSGS is rare even after thorough literature search. We propose tuberculosis especially extrapulmonary tuberculosis may lead to FSGS, which we found in our patient.

CASE REPORT

40 years not known diabetic/hypertensive female presented with low grade intermittent fever with evening rise of temperature & night sweats for last 4 months. There was no significant localising features. After 2 months of fever onset patient gradually developed generalised body swelling, associated with increased frothiness of urine. There was no hist. s/o congestive cardiac failure or cirrhosis of liver.

DISCUSSION

Our patient has been suffering from pyrexia of unknown origin with anasarca. So, our differentials would be-

- Portal hypertension complicated by Spontaneous Bacterial Peritonitis

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Editor's Comment :

- When we encounter a case of FSGS, extensive search for the etiology is mandatory for initiating appropriate therapy.
- FSGS secondary to tuberculosis infection, is one of the rarest entities reported in available literature. These subsets of patients show improvement with anti-tubercular drug therapy without addition of immunosuppressive medications.

- Infective Endocarditis with Congestive Heart Failure
- Nephritic/ Nephrotic Syndrome

Examination :

- Moon facies
- Bipedal pitting pedal edema
- Raised Jugular Venous Pressure (8cm, prominent v wave)
 - Significant Lymphadenopathy in left post triangle (2 in number, largest 3cm) & in right supraclavicular region & in central, anterior group of left axillary region & in right axillary region. They were discrete, firm, no fixity, no overlying skin changes, non tender.
 - P/A-Spleen-palpable (3cm, firm, nontender), shifting dullness present
 - Respiratory system- b/l pleural effusion
 - Chorionic Villus Sampling (CVS) - no gallop, normally audible S1S2
 - No abnormality in breast examination & in Fundoscopy.

Investigations :

- HB:10.7/ WBC:3600 (N 59L36M04E01B00)
- Erythrocyte Sedimentation Rate-107

- Ur-80
- cr-1.7 (e-GFR-37)
- LFT –WNL, ALB -2.2, Glb – 2.2
- Lipid Profile- Cholesterol-392 / TG-295 /HDL- 50
- Ft4/ TSH- 0.9/ 2.4
- Urine RE & ME- RBC-10-15 / granular cast/ protein 3+
- Urine c/s- neg.
- 24 hour urine protein -8.2g
- Integrated Counselling and Testing Centres / HBsAG /Anti Hepatitis C Virus – NR
- Sputum Acid-fast bacillus & Cartridge- Based Nucleic Acid Amplification Test - neg.
- USG W/A- Retroperitoneal Lymphadenopathy & splenomegaly, moderate ascites
- USG Doppler of spleno -portal axis: No evidence of Pulmonary Hypertension (PHT)
- Chest x Ray –b/l pleural effusion (Fig 1)



Fig 1

- 2D-ECHO-wnl
- Ascitic Fluid Study –High SAAG, cell count 90 (mainly mononuclear cells) CBNAAT- neg.
- Pleural Fluid Study –Transudative (light's criteria), ADA & CBNAAT- neg.

Differential Diagnosis :

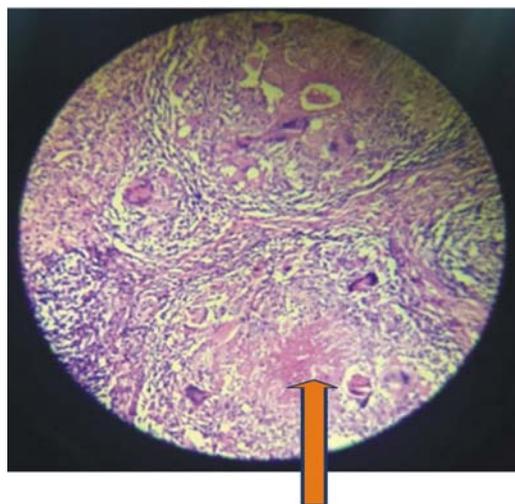
Pyrexia of unknown origin with Nephrotic Syndrome in a 40 years aged non diabetic, normotensive euthyroid patient.

Our Differentials would be —

- Connective tissue disorders- SLE, Sarcoidosis,
- Neoplastic disorder- Lymphoma
- Infective disorder- Tuberculosis
- Misc. Amyloidosis.

In Search of the Etiology, we performed —

- Excision Biopsy from supraclavicular lymph node (Fig 2)
- CBNAAT from lymph node tissue- positive
- Urine TB Polymerase Chain Reaction (PCR) - negative
- Autoimmune profile-



well formed granuloma with wide areas of caseous necrosis ie, Granulomatous lymphadenitis

Fig 2

ANA by Hep 2 Method & ANCA profile - neg
Low C3 (69.4) ,normal C4

- Renal biopsy-
Focal global glomerulosclerosis in 7 out of 15 glomeruli Immunofluorescence study was normal
Negative for congo red stain (Fig 3)

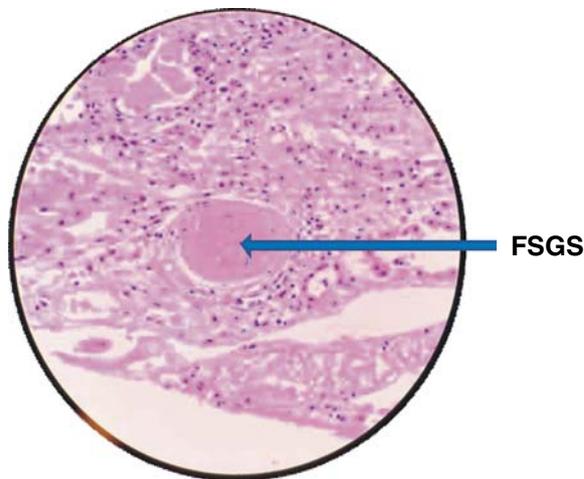


Fig 3

Provisional Diagnosis :

Tuberculous lymphadenopathy with FSGS

Treatment & Follow up:

- In view of tuberculous lymphadenopathy we started ATD
- After 6wks of therapy- the LNs regress.
Patient's clinical condition improved

24 hour urine proteinuria decreased from 8.2 gm to 1.35 gm

We continued therapy with ATD, ramipril, atorvastatin & this resulted in a partial improvement in renal function and proteinuria and regression of lymphadenopathy (Fig 4).

Repeat X-ray showed decreased pleural effusion

DISCUSSION

- Extrapulmonary Tuberculosis may occur in 10-40% of cases having myriad of manifestations
- Tuberculosis can cause renal disease in a number of ways-

- ◆ Genitourinary TB (direct invasion)
- ◆ Chronic interstitial nephritis
- ◆ Amyloidosis

• Renal involvement in Tuberculosis histologically shows epithelioid granuloma with or without caseation.

• The association of FSGS & Tuberculosis infection in the form of Extrapulmonary Tuberculosis is unique and has not been documented in the literature so far to date

• There is simultaneous existence of both FSGS and extrapulmonary tuberculosis in our patient without any preexisting conditions which might independently pre-dispose the patient to either of the two entities

• There occurs simultaneous improvement of both the entities solely with antitubercular treatment, without any immunosuppressive therapy.

• These indicates that the association may not be a mere finding but that they most probably are causally related.

CONCLUSION

- Extrapulmonary Tuberculosis is one of the aetiology of secondary FSGS



Fig 4

- Treatment with Immunosuppressive Therapy is not necessary in secondary FSGS
- Treating the cause is the mainstay of therapy, so a thorough search for the aetiology is must in all cases of FSGS

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Case Report

A Man with Progressive Swelling of Abdomen : Uncommon Presentation of a Common Disease

Avik Medda¹, Amartya Kumar Misra²

Ascites is a rare manifestation of chronic Pancreatitis. Patients usually present with progressive ascites with past history of Pancreatitis. But sometimes Pancreatic Ascites may present without any history of pain abdomen suggestive of Pancreatitis. We will discuss a case of painless Pancreatic Ascites without any history of hematemesis or melaena, pedal oedema, respiratory distress, abdominal pain or trauma. CT scan of abdomen revealed atrophic pancreas with calcification, peripancreatic collection and ascites. Amylase level in ascitic fluid was high. MRCP showed Cholecystitis with dilated common bile duct with complete loss of pancreatic duct architecture. Patient was initially managed medically followed by surgical intervention.

Pancreatitis should be suspected as etiology of progressive ascites in chronic alcoholic patients with or without typical abdominal pain as early management both medically as well as surgically is the cornerstone of treatment success.

[J Indian Med Assoc 2021; 119(11): 54-6]

Key words : Painless pancreatitis, Chronic pancreatitis, Pancreatic ascites.

Ascites is a rare presentation of chronic Pancreatitis. Patients present with progressive ascites with prior history recurrent pain abdomen. But sometimes Pancreatic Ascites may also present without any prior history of typical abdominal pain suggestive of acute or Chronic Pancreatitis. Pancreatic Pseudocyst leakage or ductal disruption are among the commonest etiologies Chronic Pancreatic Ascites. It is more common in chronic alcoholic patients. Pncreatic Ascites may present with recurrent or refractory ascites leading to confusion with malignant ascites. Here we are going to present a case of pancreatic ascites without any prior abdominal pain in an alcoholic person.

CASE REPORT

A 55-year-old non-diabetic, non-hypertensive man from West Bengal, India presented with gradually progressive distension of abdomen for past 2 months with progressive loss of weight. He had history of regular alcohol intake for past 20 years but no history of smoking. There was no history of Hematemesis or Melaena, Clay-coloured stool, Pedal oedema, Shortness of breath, Pain abdomen, Fever or Abdominal Trauma. On examination mild pallor and huge ascites were present. Vitals were stable. No Spider Navei, Venous Prominence, Palmer Erythema, Gynaecomastia or Flapping Tremor were present. Complete hemogram showed Hemoglobin (Hb) - 9.2 gm%, Total Leukocyte count - 4300 cells/ cmm, Platelet count - 2,30,000 cells/ cmm. Liver Function Test

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Editor's Comment :

- When an alcoholic patient presents with Ascites, Pancreatic Ascites should be kept in mind as a differential beside more common entities like Chronic Liver Disease or Tuberculosis.
- Rarely patients may present as painless abdominal distension and even without any past history of Acute or Chronic Pancreatitis.

(LFT) showed Bilirubin (total) – 0.3 mg/dL, Albumin - 3.2 gm/dL, Globulin - 3.4 gm/dL, Serum Glutamic-Oxaloacetic Transaminase (SGOT) – 29 IU/L, Serum Glutamic-Pyruvic Transaminase (SGPT) – 11 IU/L, Alkaline Phosphatase – 158 IU/L, Gamma Glutamyl Transferase – 36 U/L. Enzyme-linked Immunosorbent Assay (ELISA) for HIV I & II was non reactive, Hepatitis B Surface Antigen (HBsAg) and anti HCV were also non reactive. Ultrasonogram of whole abdomen showed normal size and echotexture of Liver, Spleen- 9.5 cm, diameter of Portal vein - 11.2 mm and huge ascites, no pseudocyst of pancreas. Ocult blood in stool was absent. Upper GI endoscopy did not show any varices or portal gastropathy. Ascitic fluid study revealed, Cell count – 200/ cmm , 95% Lymphocytic, Total Protein – 3.1 gm/dL, Sugar – 85 mg/dL (Corresponding blood sugar was 110 mg/dL), Serum Ascites Albumin Gradient (SAAG) – 0.9, Adenosine Deaminase (ADA) – 6.0 U/L, Cartidge Based Nucleic Acid Amplification Test (CBNAAT) – negative. Patient was having shortness of breath for which Therapeutic Paracentesis was done which was followed by rapid reaccumulation of fluid. Thus repeated ascitic fluid Paracentesis had to be done. Malignant ascites was suspected and for which tumour markers were ordered. Tests revealed only mild elevation of CA 19.9 (serum α -feto protein - 5.9 ng/ml, β -hCG – 2.1 mIU/ml, Carcino Embryonic Antigen (CEA) – 1.61 ng/ml,

CA19.9 –337.18 U/ml). For further evaluation of organ involvement, contrast enhanced CT scan of whole abdomen was done, which ultimately clinched the diagnosis, showing atrophic pancreas with calcification, peripancreatic collection and ascites (Fig 1). Ascitic fluid amylase was found to be very high (5379 U/L). Serum amylase was 340 U/L [Normal range 40-120 U/L]. MRCP showed Cholecystitis with dilated common bile duct traced upto distal end with complete loss pancreatic duct architecture (Fig 2). Patient was treated conservatively with nothing per mouth, intravenous fluid and antibiotics, diuretics, therapeutic paracentesis and octreotide. After initial stabilisation, patient was referred to the Gastroenterological Surgery Department for Definitive Surgical Management and was underwent Pancreatic

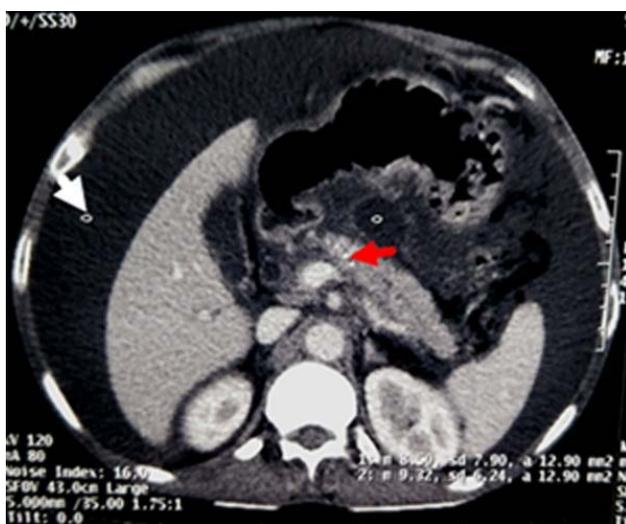


Fig 1 — Contrast enhanced CT scan of whole abdomen showing huge ascites (white arrow), atrophic pancreas with loss of architecture and multiple hyper-dense opacities in the body and head of pancreas suggestive of calcifications (red arrow)



Fig 2 — MRCP showing dilated common bile duct traced up to distal end (white arrow) with loss of normal pancreatic duct architecture suggestive of duct disruption (red arrow)

Duct Stenting and Reconstructive Surgery. Patient was counselled for alcohol cessation and advised for follow-up regularly. After 3 months in the follow-up clinic, patient was found in stable condition without any significant ascites or persisting pain abdomen.

DISCUSSION

Ascites is one of the commonest manifestations of Chronic Liver Disease and is usually consequence of the two of its common entities- portal hypertension and hepatocellular failure. Pancreatitis is one of the rare etiologies of ascites in patients with habit of long-standing alcoholism and prior history of pain abdomen. But Pancreatic Ascites without any prior history of pain abdomen is a rarest option. Pancreatic ascites is characteristically exudative in nature, with high amylase concentration in ascitic fluid (more than 1000 IU/L) and protein concentration of more than 3 gm/dL² that differentiate it from Malignant Ascites and ascites secondary to Cirrhosis of Liver or Tuberculosis. Pancreatic ascites is a rare entity and is reported in around 3-4% of patients with chronic pancreatitis and 6-14% of patients with Pseudocyst of Pancreas^{3,4}.

Common entities causing Pancreatic Ascites are Chronic Pancreatitis, Ductal Lithiasis, Ampullary Stenosis, Pancreatic Trauma, Ductal Disruption and Cystic Duplications of Biliopancreatic Ducts². Pancreatic ascites is more common in men (male : female = 2:1) and between the age of 20-50 years². The clinical manifestations are progressive ascites, weight loss with abdominal pain. Pancreatic ascites should be thought as differential in patients with progressive ascites with history of Alcoholism, Chronic Pancreatitis or Abdominal Trauma⁵.

Therapy for Pancreatic Ascites has many controversies in part of both Medical as well as Surgical management⁶. No randomized control studies are available regarding management of the condition probably due to the rarity of the entity. Though no consensus is available on the management, Chebli *et al* proposed that the management should be guided by the Ductal Anatomy defined by the Endoscopic Retrograde Pancreatography (ERCP). Conservative therapy includes the somatostatin analogues^{8,9} and keeping the patient Nothing Per Mouth (NPM) to reduce pancreatic secretion. Initial continuous octreotide infusions followed by subcutaneous injections may be suggested. Patient may be managed with repeated ascitic fluid drainage for symptomatic relief and parenteral nutrition. Long acting Intra-muscular Octreotide may be given once a month as maintenance therapy.

Surgical intervention is also recommended when there is no response to conservative medical management for consecutive 3 - 4 weeks. Recurrence rate has been reported around 60% in patients undergoing surgical intervention without prior ERCP^{10,11}. Mortality rates have been reported to be comparable with both surgical and medical therapies (15-25%)¹².

CONCLUSION

Pancreatic ascites should be considered in the differentials of progressive ascites in chronic alcoholic patients with or without typical pain abdomen suggestive of pancreatitis as early diagnosis and treatment leads to favorable outcome.

ACKNOWLEDGEMENT

We acknowledge the encouragement shown by the Director of School of Tropical Medicine, Kolkata and am thankful to the Scientific Research and Ethical Committee, School of Tropical Medicine, Kolkata for giving us a chance to publish the paper. Ultimately it is the patient, we have the opportunity to attend and care, taught us the lessons on the case and we gratefully acknowledge his consent.

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Case Report

Autoimmune Encephalitis (Anti NMDA Receptor Antibody Encephalitis) — Our Experience

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Autoimmune Encephalitis is an immune mediated Neurological Disorder which was recognized only in the 21st century. Neuroimmunology is one arena of Neurology which is amenable to effective management if identified early. There are many types of Autoimmune Encephalitis with unique clinical manifestations. N-methyl-D-aspartate Receptor (NMDAR) encephalitis can present with subacute onset behavioral disturbances, movement disorders, cognitive decline and new onset seizures which is refractory to antiepileptic drugs. It is commonly seen in young females sometimes in association with ovarian tumors. Immunotherapy when started early in the course of the disease usually causes significant improvement of neurological symptoms. We treated two young females with NMDAR Encephalitis who improved well with Immunotherapy. Both of the patients presented with recent onset behavioral disturbances and seizures which was refractory to antiepileptic drugs.

[J Indian Med Assoc 2021; 119(11): 57-9]

Key words : Autoimmune encephalitis, New onset refractory seizures, Behavioural disturbances.

Neuro immunology is considered to be a unique subspecialty of Neurology, wherein, timely diagnosis and appropriate treatment of the neurological syndrome leads to significant recovery. It is imperative to consider an immunological pathogenesis, when encountered with any form of acute or subacute neurological disorder. We report the following two cases of autoimmune encephalitis (Anti NMDA receptor antibody encephalitis) to emphasize the need for high index of suspicion to diagnose this rare treatable entity. Both of our patients responded exceptionally well to timely immunotherapy.

Case 1 :

A 21-year-old female with no significant past history presented with history of altered behaviour in the form of apathy and mutism of 2 weeks duration followed by multiple episodes of complex partial seizures with secondary generalisation over a period of 1 week. On examination, she was found to be in a state of post ictal confusion. Cranial nerves, motor system, sensory system, cerebellum and extrapyramidal system were normal on examination. There were no meningeal signs. Patient was started on multiple anti epileptic drugs because of recurrent episodes of seizures. She was on phenytoin 300mg, levetiracetam 1500mg,

Editor's Comment :

- The clinical manifestations of Autoimmune Encephalitis are diverse and are often multifocal.
- Detection of a neural specific autoantibody serves as a marker of neurologic autoimmunity.
- Timely recognition and appropriate immunotherapy ensures a better prognosis in patients with Autoimmune Encephalitis.

phenobarbitone 120 mg and clobazam 20 mg per day. Based on the history of recent onset behavioral disturbances and new onset seizures, the possibility of Viral Encephalitis / Autoimmune Encephalitis was made. Laboratory parameters were within normal range. Magnetic Resonance Imaging (MRI) of the brain did not show any abnormality. EEG showed (black arrow) left Temporal Intermittent Rhythmic monomorphic delta range slow waves (TIRDA)(Fig 1).

CSF analysis was done which was acellular with normal sugar and protein. Cerebrospinal Fluid (CSF) and serum viral antibody profile including Herpes Simplex Virus (HSV) was negative. CSF NMDAR antibody was positive. Patient was started on intravenous methylprednisolone 1 gm IV once daily for 5 days. She also received IV antibiotics and IV acyclovir for 14 days.

A course of intravenous immunoglobulin 20 gram per day was given for 5 days. During the course in hospital patient had disinhibited behavior, anger outbursts, inappropriate laughter and other weird behavioral disturbances. Following treatment, patient gradually improved with no further episodes of seizures. The patient's behavioural disturbances partially improved over the next few weeks. Patient was also given weekly Rituximab 500mg for 4weeks. She is on regular follow up.

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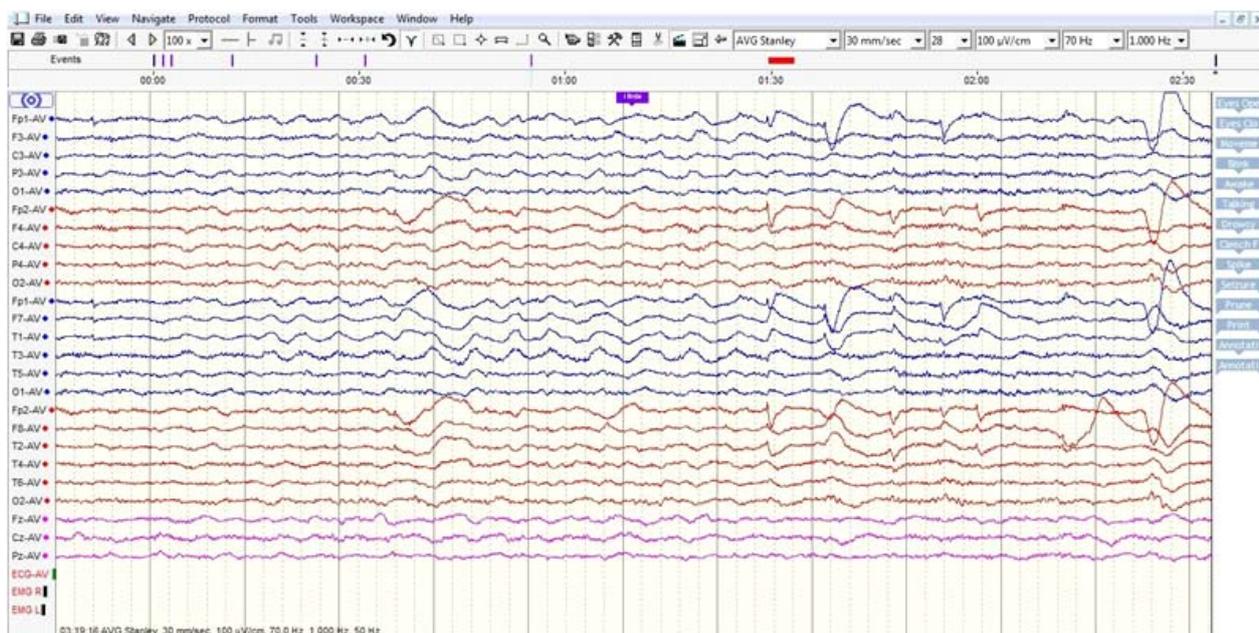


Fig 1 — EEG showed (black arrow) left temporal intermittent rhythmic monomorphic delta range slow waves (TIRDA)

Case 2 :

A 13-year-old girl presented with history of behavioral disturbances in the form of insomnia, excess shouting, anger outbursts, episodes of mutism and temper tantrums followed by fixed gaze to left side with epileptic partialis continua involving left upper limb. On examination, patient had gaze preference to left side with recurrent clonic twitching of left forefinger and left great toe with dystonic posturing of left foot. Patient was initiated on multiple Automated External Defibrillator (AED's) since she had relentlessly continuing left focal seizures. She was on Phenytoin 300mg, Levetiracetam 2000 mg, Lacosamide 200mg and Clobazam 20 mg per day with Midazolam infusions in between. Based on the clinical features of new onset uncontrolled seizures and associated behavioral/personality disturbances, a diagnosis of viral/autoimmune Encephalitis was made. Laboratory parameters were normal. MRI Brain was normal. EEG showed medium to high amplitude polymorphic slow waves in delta range over right hemisphere (Fig 2). CSF and serum viral profiles including HSV was negative. CSF NMDAR and serum NMDAR antibodies were positive. Patient was initiated on intravenous Methylprednisolone for 5 days followed by a 5 day course of intravenous immunoglobulin. We noted marked improvement of behavioral disturbances and focal seizures over a period of 2weeks following treatment. Patient was also given weekly Rituximab for 4 weeks. The patient is on regular follow up.

DISCUSSION

We encountered two young females with NMDAR

Encephalitis who had similar types of presentation in the form of new onset recurrent seizures and behavioral disturbances which responded well to immunotherapy. Autoimmune Encephalitis is a treatable disease, which has to be recognized early¹. The clinical symptomatology of this group of diseases ranges from very subtle symptoms to severe manifestations like status epilepticus and psychosis². Anti-N-Methyl-D-Aspartate Receptor Encephalitis was initially reported by Dalmau *et al* in 2007. It is commonly seen in children and young adults². The Pathophysiological mechanisms by which these autoantibodies against NR1 subunit of NMDAR cause Central Nervous System (CNS) damage is being unraveled³. The role of complements is uncertain. The synthesis of NMDAR antibodies inside the CNS has been demonstrated in several studies⁴.

A viral prodrome invariably precedes the disease. Infection with mycoplasma or other microbes is found to herald certain cases of autoimmune Encephalitis⁵.

One third of patients with herpes simplex Encephalitis develop NMDAR Encephalitis, suggesting a secondary autoimmune response. The disease evolves in stages. Stage 1 is characterized by fever and headache. During stage 2, patient develop mild anxiety, irritability and anger outbursts. On reaching Stage 3, patients develop seizures, psychosis and severe disability. MRI brain is normal in the majority of patients. About one third of patients may have non specific cortical and subcortical hyperintensities. CSF analysis may show increased proteins and lymphocytosis. EEG shows focal epileptiform discharges or generalized slowing.

The sine qua non EEG feature of "delta brush" is rare. The diagnosis is made by detecting NMDAR antibodies

Short Communication

Physician's Role — The Challenging Task of Balancing Multiple Responsibilities

Samik Kumar Bandyopadhyay¹

A doctor in the new millennium must engage in a host of activities other than direct clinical care. These include administrative responsibilities as a leader or a manager, teaching roles for students, trainees and the society and an effective communicator at large. The professional demands of a changing world often needs a relook at the resources for ongoing training. To prepare for the professional needs, the doctor needs to understand the implications of the role he/she is involved in the current position, prepare for upcoming challenges and enhance the sustainability of a successful career.

[*J Indian Med Assoc* 2021; 119(11): 60-1]

Key words : Management, Leadership, Communication, Training.

The millennial shift in the doctor's role has placed the modern physician in a unique position that keeps evolving continually. It has long been accepted that along with the role of a care giver, the physician must take on the responsibilities of a teacher, a leader, and a manager. The formal nature of medical education often leaves the doctors with less than adequate skills in their arsenal when the spectrum of expectation in these roles are accounted for. The challenging demands of the job at hand often tends to overwhelm the resources available – most of the times the doctors consider the sweet and not-so-sweet experiences as part of learning on the go. This is frequently stressful and leads to an unfavourable work life balance. There is a price to pay, as many have said before.

Medicine is a profession that offers three broad incentives – dignity, job satisfaction and money. The professional hierarchy with the honorific prefixes, the social bearings, exposure to the niceties of life may all be accounting for the dignity that comes along with the role. Satisfaction in a current job role is more elusive – it may depend on the hours of work, the pattern of work, the commute involved and a million other factors including the environment and emotional intelligence. When it comes to money, things can often get fuzzier as there may be no endpoint to what is 'enough'. Importantly, the earnings and expenditure need to be titrated against the norms of social security and family responsibilities. The importance of each aspect to an individual is not universal when personal aspirations are considered. They may not be static

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throughout life and interest in each aspect may well wax and wane. However, the necessity of considering these aspects in defining professional success for oneself remains undeniable.

It is on the background of these aspects the role of the physician has continued to evolve. It is important for the present generation to appreciate these vital aspects in honest retrospection while defining the evolving demands.

Leader and Manager : At times the same but not always :

The doctor is often expected to shift fluidly into a role he had not expected to be in. It is important to understand the "Peter Principle" – a concept in management¹. This is based on the observation that in a hierarchy, a competent and successful person will get promoted to the next level to perform a job for which they are incompetent, as one set of skills may not readily be transferable to other. Looking back, a successful student will start his day of internship as an incompetent one, only to transform into a competent Junior Doctor expected to start his/her residency and the story keeps repeating over and over. The dynamics of the profession makes it imperative for the physician not only to keep updating but also accumulate soft skills on the way – both formal and informal trainings are beneficial.

Whether it is in the primary care or tertiary care, whether it be Government Sector or the corporate one, a doctor is just not an isolated entity – he is one of the most fundamental persons in an interactive group of individuals with varying roles in the team dynamics. Prioritisation of precious resources, including time and organising tasks into achievable, time bound subsets is uniquely tied to his job profile. Quite often, he may be interacting and motivating his team (often a group

of trainees) and setting directions, both holistically and in material terms, fulfilling the role of a leader. At other times, he may be engaged in an instructive role, planning out weekly or monthly activities (including clinics and theatre lists), balancing resources (financial or human), thus taking on the garb of a serious manager.

While creating a vision as the leader, doctors often set goals as the manager at the same time – they find themselves frequently tasked with achieving the short-term goals in the mould of a manager while assessing the long-term impact in the role of a leader. Interestingly, the pandemic has managed to bring out the best of such capabilities across the globe – amidst a frantic firefighting, setting and achieving medium- and long-term targets have always been a part of the plan. Organisational capabilities as a manager and a far-sighted adaptability as a leader often need to be fused into the same role.

Teacher – An ever-widening role :

The Medical schools have a unique process of turning the most reticent of students into accidental teachers. Informal teaching and sharing of knowledge often transcend the yearly batches and rarely follows any imposed restrictions. Thousands of medical romances have bloomed uncharacteristically from the Gargantuan Medical Books. The pandemic has accelerated an ongoing trend towards use of virtual platforms like Zoom and Teams for teaching and training along with ever increasing use of blogs, podcasts, vodcasts, interactive white boards, wikis, simulations and audience response systems². While embracing the digital revolution, the Medical Teacher is expected to be calm yet enthusiastic, knowledgeable, and approachable, logical yet passionate, a learner and a mentor at the same time – a difficult proposition indeed. In essence, to serve as a role model for the students and trainees, a Medical Teacher must be flexible enough to reinvent himself/herself according to the teaching needs.

It remains a fundamental responsibility of the doctor to provide a Clinical Learning Environment for the Students and Trainees, who may be medical, nursing, or allied healthcare specialists in the make. This would put the onus on three different aspects – clinical work, learning process and the environment per se³. The demands of this process means accounting for the barriers of communication (Physical like a large desk at times, language barriers, cultural barriers etc), psychological and social aspects (like a rigid hierarchy, age differences preventing the sharing of outlook etc).

Doctor as a Communicator :

In the context of modern medicine, the art of communication plays an exceptionally vital role. In the

yesteryears, communication was primarily face to face and usually within a known sphere of activity. At times, the print media or the television would draw information, advice or inspiration depending on the situation at hand. The digital age has often brought the doctor away from the traditional teaching environment to a myriad of other platforms - the social media, virtual classrooms, podcasts etc. To be effective and successful in these newer vistas, the sublime art of communication is an essential survival skill. It all starts from being able to be a good listener and acquiring the powers of empathy and confidence. Conveying respect to the involved team, often using non-verbal means (body language for example), having an open mind, being able to be clear, concise and personable are especially important. Quite frequently, doctors tend to imbibe the skills from their peers and role models (sometimes, their weaknesses as well) but often a structured system helps to a great extent in improving the capabilities needed for the job.

What Lies Ahead ?

It may be a good idea to accept that the rigours of the profession may only increase. The existential problems of the current World was crisply summarised in the Leadership Theories of Warren Bennis and Burt Nanus in 1987 – VUCA. It is an appropriate acronym that stands for Volatility, Uncertainty, Complexity and Ambiguity. Being prepared is no doubt the best way forward to take on the challenges of a long journey where the incentives may not always be abundant. Introduction of the basic concepts of communication, management and teaching at the undergraduate curriculum is always helpful if the steps are followed up with structured formal and informal training programmes over the years of residency and professional practice. Some doctors will be privileged enough to have worked in settings and teams which allow them to imbibe the skills as part of learning on the go. This may not hold good for a significant number of their professional colleagues. The introduction of courses and training programmes may be of significant help for this group. Acquisition of soft skills often lead to professional expertise and resourceful exploitation of the hard-earned clinical skills – the final aim of a successful career.

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Special Article

Future of COVID-19

Ravi Wankhedkar¹

Indian Scenario :

After the second wave, the daily average of COVID-19 cases in India is spiraling down, even though there still are isolated outbreaks and a rising positivity rate recorded in some states. However, despite this, there's some positive silver lining, which is the growing pace of vaccination in the country. While we may not be able to bid goodbye to COVID-19 as yet, it might be the time the viral outbreak may have reached a state of 'endemicity' in the country, given the rather low levels of transmission right now and the already largely exposed population in the country. But, with the virus very much an active threat and possibilities of a potentially threatening third wave looking like an imminent threat, what does endemicity mean, in terms of COVID-19 spread and how concerned should we be?

Ever since mutant variants of the virus have wreaked havoc and lowered the efficacy of vaccines, experts have pinpointed that achieving herd immunity or removing COVID-19 from the World, altogether may not be actually possible. While we do know that certain mandates, such as testing, mask hygiene, distancing would still need to be followed till we know there's a low-graded risk, living while knowing that there's a virus forever could be very well a reality to acclimatize ourselves too.

While learning to live with COVID-19 forever does mean that the virus may never ever go away, however, it does mean that the virus, over time, may become less threatening and as higher rates of immunization are achieved, the virus would have fewer chances of spreading or spell severe outcomes, as we are seeing today. Several experts have also stressed that instead of trying for a zero-COVID-policy, transitioning from a pandemic to an endemic is the best probable scenario we may have currently.

High immunization rates and vaccination speeds are needed to provide peak protection and limit COVID from spreading. As we move into the future course of months, where there's a possibility of seeing more mutations coming up, the current vaccines may be

upgraded, or subjected to changes, which could help them offer more protection and efficiency than we currently have. There's also talk of booster shots right now, which may be suggested for those who are immuno-compromised.

In the future, COVID vaccination may also become an annual affair, much like flu vaccination and thus, with added immunity, it would our best shot of defense to mitigate the risks of COVID-19.

Global Scenario :

The COVID-19 pandemic has been met by unequal responses in different countries and led to unequal impacts with populations in Europe, the USA and Latin America disproportionately impacted.

Science has uncovered much about SARS-CoV-2 and made extraordinary and unprecedented progress on the development of COVID-19 vaccines but there is still great uncertainty as the pandemic continues to evolve. COVID-19 vaccines are being rolled out in many countries but this does not mean the crisis is close to being resolved. We are simply moving to a new phase of the pandemic.

What emerges next will partly depend on the ongoing evolution of SARS-CoV-2, on the behaviour of citizens, on Governments' decisions about how to respond to the pandemic, on progress in vaccine development and treatments and also in a broader range of disciplines in the sciences and humanities that focus both on bringing this pandemic to an end and learning how to reduce the impacts of future zoonoses and on the extent to which the International Community can stand together in its efforts to control COVID-19. Vaccines alone, unless they achieve high population coverage, offer long-lasting protection and are effective in preventing both SARS-CoV-2 transmission and COVID-19, will not end the pandemic or allow the World to return to "business as usual". Until high levels of global vaccine-mediated protection are achieved across the World, it could be catastrophic if measures such as mask wearing, physical distancing and hand hygiene are relaxed prematurely.

Countries, communities and individuals must be prepared to cope in the longer-term with both the demands and the consequences of living with such essential containment and prevention measures.

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Many factors will determine the overall outcome of the pandemic. A Nationalistic rather than Global approach to vaccine delivery is not only morally wrong but will also delay any return to a level of “normality” (including relaxed border controls) because no country can be safe until all countries are safe. SARS-CoV-2 could continue to mutate in ways that both accelerate virus transmission and reduce vaccine effectiveness.

Vaccine hesitancy, misinformation and disinformation could compromise the global COVID-19 response.

Naive assumptions about herd immunity, given the appearance of new and challenging SARS-CoV-2 variants, could seriously risk repeated outbreaks and recurrences. SARS-CoV-2 can probably never be Globally eradicated, because of its presence in many animals (including cats and dogs) and because of incomplete vaccine coverage and variable degrees of immunological protection.

Hence, ongoing strategies to deal with the endemic presence of SARS-CoV-2 in populations over the long term will be needed. Furthermore, we do not yet know if and when, revaccination with current or new COVID-19 vaccines will be required since the duration of immunological protection and the efficacy against emergent SARS-CoV-2 variants remain unknown. With such uncertainties, we should not assume that recent scientific progress on COVID-19 diagnostics, vaccines and treatments will end the pandemic. The world is likely to have many more years of COVID-19 decision making ahead—there is no quick solution available at present.

The decisions of global agencies and governments, as well as the behaviors of citizens in every society, will greatly affect the journey ahead. There are many possible outcomes. At one extreme is the most optimistic scenario, in which new-generation COVID-19 vaccines are effective against all SARS-CoV-2 variants (including those that may yet emerge) and viral control is pursued effectively in every country in a coordinated effort to achieve global control. Even with International Cooperation and adequate funding, this scenario would inevitably take a long time to achieve. The COVAX initiative is just an initial step towards addressing vaccine equity and global coordination for vaccine access, especially for lower income countries.

At the other extreme is a pessimistic scenario, in which SARS-CoV-2 variants emerge repeatedly with the ability to escape vaccine immunity, so that only high-income countries can respond by rapidly manufacturing adapted vaccines for multiple rounds of

population re-immunization in pursuit of National control while the rest of the world struggles with repeated waves and vaccines that are not sufficiently effective against newly circulating viral variants. In such a scenario, even in high-income countries, there would probably be repeated outbreaks and the path to “normality” in society and business would be much longer and there are many other intermediate or alternate scenarios.

Countries that have kept SARS-CoV-2 in check and countries where there are high levels of viral transmission will in time all probably reach a similar destination, even though their paths to arrive there will be quite different, because no countries can remain permanently isolated from the rest of the World. Unfortunately, countries working in isolation from each other and from Global Agencies will prolong the pandemic. A nationalistic rather than a global Approach to COVID-19 vaccine availability, distribution and delivery will make a pessimistic outcome much more likely. Additionally, unless countries work together to scale up prevention efforts, the risk of other pandemics, or other trans boundary disasters with similar consequences, including those fuelled by climate change, will remain a constant threat.

The International Science Council (ISC), as the independent, Global voice for science in the broadest sense, believes it is crucial that the range of COVID-19 scenarios over the mid-term and long-term is explored to assist our understanding of the options that will make better outcomes more likely. Decisions to be made in the coming months need to be informed not only by short-term priorities but also by awareness of how those decisions are likely to affect the ultimate destination. Providing such analyses to policy makers and citizens should assist informed decision making.

In developing its COVID-19 Scenarios Project, the ISC has consulted with WHO and the UN Office for Disaster Risk Reduction. The ISC has established in February, 2021, a multidisciplinary Oversight Panel made up of globally representative world experts in relevant disciplines to work with a technical team to produce the scenario map. The Oversight Panel will report within 6–8 months to the Global Community on the possible COVID-19 scenarios that lie ahead over the next 3–5 years and on the choices that could be made by Governments, agencies and citizens to provide a pathway to an optimistic outcome for the World.

There is a realistic expectation that the global effort in vaccination will bring the pandemic caused by Severe

Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) under control. Nonetheless, uncertainties remain about the type of long-term association that the virus will establish with the human population and in particular, whether Corona Virus Disease 2019 (COVID-19) will become an endemic disease. Although the trajectory is difficult to predict, the conditions, concepts and variables that influence this transition can be anticipated. Persistence of SARS-CoV-2 as an endemic virus, perhaps with seasonal epidemic peaks, may be fuelled by pockets of susceptible individuals and waning immunity after infection or vaccination, changes in the virus through antigenic drift that diminish protection and re-entries from zoonotic reservoirs. Here, we review relevant observations from previous epidemics and discuss the potential evolution of SARS-CoV-2 as it adapts during persistent transmission in the presence of a level of population immunity. Lack of effective surveillance or adequate response could enable the emergence of new epidemic or pandemic patterns from an endemic infection of SARS-CoV-2. There are key pieces of data that are urgently needed in order to make good decisions; we outline these and propose a way forward.

Main Three Possible Scenarios of the Future of COVID-19 :

The first—and most worrisome—scenario is that we will not gain rapid control of this pandemic and thus will face a future with ongoing manifestations of severe disease combined with high levels of infection that, in turn, could foster further evolution of the virus. Vaccinations and previous infection could achieve long-term herd immunity but we will need a very broad application of vaccines Worldwide combined with comprehensive disease surveillance by accurate and readily available diagnostic assays or devices.

A second and more likely scenario is the transition to an epidemic seasonal disease such as Influenza. Effective therapies that prevent progression of COVID-19 disease (for example, monoclonal antibodies that reduce hospitalization and death by 70–85%) may bring the burden of SARS-CoV-2 infection to levels that are equivalent or even lower than influenza. However, we should remember that the annual mortality burden of influenza, in non-pandemic years, is estimated to be between 250,000 and 500,000 deaths with up to 650,000 all-cause deaths globally, comprising around 2% of all annual respiratory deaths (two thirds among people who are 65 years and older). This is an extremely important health burden and equates to a relatively 'optimistic' view of the future of the COVID-19 pandemic.

A third scenario is the transition to an endemic disease similar to other human Corona Virus Infections that have a much lower disease impact than influenza or SARS-CoV-2. There is, however, limited data on the Global burden of disease by Common Human Corona Viruses and as noted in above, it is not possible to predict with confidence whether further adaptations of SARS-CoV-2 to humans will increase or decrease its intrinsic virulence.

To better predict which scenario is likely to emerge and to better equip the world with an appropriate response, we propose several key questions that need to be answered and critical tools that need to be developed. These comprise gaps in our knowledge in terms of epidemiology, immunology and virology and missing surveillance, prophylactic and therapeutic tools.

This pandemic has shown both the importance of initiatives in individual countries and the interdependence of the world and the necessity of Global Cooperation for pandemic control. It is the investment by a limited number of countries that has led to the biomedical discoveries that have brought forward the tools to interrupt the spread of the pandemic. Yet, the lack of International structures for the implementation of these tools has brought into focus the disparities between advantaged and disadvantaged groups both within countries and between countries. This highlights the current inadequacies in healthcare delivery systems and access to new biomedical interventions. Global health leaders will need to be vigilant with respect to the trajectory of SARS-CoV-2 in the near future while assessing the strategies and approaches used in the pandemic to develop more effective structures and processes to ensure a more effective and equitable response for the future.

The Next Pandemic :

The COVID-19 pandemic was not the first to devastate the World and will not be the last.

The COVID-19 pandemic felt for many of us like it came out of the blue but scientists have long been sounding the alarm about a potential pandemic from a Corona Virus.

We already had warnings with the SARS and MERS outbreaks, both caused by Corona Viruses and both spilled over from animals into humans. Given the way people continue to encroach on animal habitats, trade wildlife and eat bush meat, it is increasingly likely that zoonotic diseases that come from animals will cause future pandemics.

This already happens more often than you might

think. Since the 1940s more than 330 emerging infectious diseases have been identified, of which 60% were zoonotic. And when a new infectious disease does emerge, human migration, population growth, rapid global travel, climate change Urbanisation and dense Urban slums can all hasten its spread. Given that more people are living in closer proximity to each other than ever before and that normally more than a billion people cross international borders each year, it has never been easier for outbreaks to escalate and spread Globally.

With the current pandemic, research carried out in response to previous Corona Virus outbreaks and developments in vaccine technologies gave us a head-start that meant that COVID-19 vaccines could be developed rapidly. Even so, at the outset we had limited National Systems for case detection and tracking of epidemic spread. The complete lack of treatments or existing vaccines meant that in the year that it took to develop vaccines, millions lost their lives to COVID-19.

R&D tends to focus on immediate threats and often on drugs, vaccines or diagnostics that are most profitable, which explains why many diseases identified by World Health Organization (WHO) as having a high potential to cause future pandemics are currently being neglected. Many of these threats affect low- and middle-income countries and have little or no research and development ongoing. This is dangerous and means that if any of these diseases turn pandemic, we could once again be caught off guard. Millions of lives could be lost.

Future Potential Pandemics?

- Nipah virus ?
- Ebola ?
- Chikungunya ?
- H5N1 and H7N9 influenza ?
- Yellow fever ?
- Marburg ?
- Lassa fever ?
- Crimean-Congo Haemorrhagic Fever ?
- Hantavirus ?

Conclusion :

We need to recognize the close interactions between health and wellbeing of animals, humans and the environment.

COVID-19 pandemic and future pandemics are likely to emerge from ecological processes such as climate change, loss of biodiversity, anthropogenic social processes (eg, corporate interests, culture and globalization) and world population growth. Intervention would therefore require modifications or dampening these generators :

- The COVID-19 pandemic wasn't the first to devastate the world and it won't be the pandemic
- The COVID-19 pandemic wasn't the first to devastate the world and it won't be the last.
- The COVID-19 pandemic wasn't the first to devastate the world and it won't be the last.

The Next Pandemic :

The COVID-19 pandemic wasn't the first to devastate.

Drug Corner

Revisiting the Efficacy and Safety of Ranitidine

Akash Shukla¹, Vijay Kher²

Ranitidine, a competitive antagonist of histamine-2 receptors, has been widely prescribed for the treatment of peptic ulcer disease and mild to moderate reflux esophagitis for more than twenty years now. With its well-established tolerability and efficacy profiles, ranitidine is a preferred agent for initiation as well as maintenance of treatment in gastroduodenal conditions. Continuous maintenance treatment with ranitidine for up to nine years is known to prevent ulcer recurrence in more than 80% of patients with duodenal ulcer disease. Overall, ranitidine is well tolerated, and adverse and serious adverse events are rare with the use of ranitidine. Common ranitidine related adverse effects include headache, dizziness, diarrhea, and fatigue. None of these side effects require discontinuation of treatment and are generally self-limiting. Ranitidine is safe for use in elderly, pregnant women, and children. Given the current situation regarding the unacceptable levels of N-Nitrosodimethylamine, a probable human carcinogen, in ranitidine formulations, there are concerns about the clinical utility of ranitidine. In this review, we describe the efficacy and safety of ranitidine and the concerns for safety with the continued use of ranitidine. Given the widespread evidence for efficacy and safety, the concerns for safety with N-Nitrosodimethylamine in ranitidine formulations should be addressed with appropriate analytical assessment and judicious use.

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Key words : Ranitidine, peptic ulcer disease, efficacy, safety, cancer.

Introduced in 1981, ranitidine is a competitive antagonist of histamine-2 (H₂) receptors that reduces gastric acid secretion. Ranitidine has been used in the short-term treatment of gastro-esophageal reflux disease (GERD) and endoscopically diagnosed erosive esophagitis, and in the maintenance therapy for duodenal or gastric ulcer at reduced dosage and erosive esophagitis. Short-term treatment with ranitidine is also effective in active duodenal ulcer or benign gastric ulcer, pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome and systemic mastocytosis). Ranitidine is extensively used in the management of these conditions with a key goal of reducing gastric acid secretion. It was one of the medicines after antibiotics to have had a profound impact in clinical practice. Given this widespread use, ranitidine is listed in the WHO model list of essential medicines¹. Increased gastric acid secretion is a common clinical challenge presenting as either a non-specific complaint like heartburn or as a manifest inflammation or ulceration. Given the changing lifestyle with poor dietary choices and increasingly sedentary habits, increased gastric acid secretion is widely prevalent.

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Editor's Comment :

- Ranitidine enables a simple approach to reduce gastric acid secretion with rapid and reliable effect and reduced risk of recurrence.
- Ranitidine is safe for use in children, elderly, and pregnant women.
- More recent studies support no association of ranitidine with the risk of cancer.
- The proven efficacy and tolerability of ranitidine since its introduction over twenty years ago will ensure its continued use in the treatment of gastroduodenal conditions.

Ranitidine, with an effective suppression of acid secretion, is the preferred agent for reducing gastric acid secretion in clinical practice. The evidence suggests an excellent safety profile and a favorable risk/benefit ratio for ranitidine²⁻⁴. However, recently concerns have been raised from the safety point of view associated with ranitidine. This has challenged the clinical utility of ranitidine in the management of acid-peptic disorders. In this paper, we review the clinical efficacy and safety profile of ranitidine to reiterate the beneficial outcomes with ranitidine in peptic disorders. We also discuss here the current evidence and controversies published for the ranitidine formulations and how this could possibly impact the therapeutic utility of ranitidine in routine clinical practice for adults and children.

Efficacy of Ranitidine :

Ranitidine has a good efficacy in the management of gastroduodenal conditions. Ranitidine (150 mg twice daily for 6 weeks) is effective in reducing the frequency

and severity of heartburn and improving the endoscopic morphology of esophageal mucosa in gastroesophageal reflux disease⁵. Ranitidine has comparable efficacy to rabeprazole, a proton pump inhibitor, when used as an on-demand therapy for relieving symptoms associated with Non-erosive Reflux Disease (NERD). In a 4-week, prospective, randomized, open-label study in 83 patients with NERD, there was no significant difference in the subjective global symptom relief between the rabeprazole (n=40) and the ranitidine (n=36) groups (71.4% versus 65.4%, respectively; P = 0.9). There were comparable results for quality of life, mean numbers of pills used, and mean number of medication-free days for ranitidine and rabeprazole⁶. Combination of ranitidine with proton pump inhibitors is said to be superior to single drug treatment in laryngopharyngeal reflux⁷.

Ranitidine is effective in erosive esophagitis. In a double-blind, placebo-controlled study in 342 patients with erosive esophagitis, ranitidine (150 mg and 300 mg four times daily) had significantly higher healing rates of 83% and 81%, respectively for the two doses and 58% for placebo at 12 weeks. The frequency, severity of heartburn and weekly intake of antacids were significantly reduced in the ranitidine arms and both doses were equally effective. Both doses demonstrated a rapid onset of action with symptom relief within 24 hours of medication intake⁸. Ranitidine (75 mg) is also effective in preventing and decreasing symptoms of heartburn when administered 30 minutes prior to intake of a heartburn-provoking meal⁹.

Ranitidine is a commonly prescribed co-medication with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as it helps to reduce the dyspepsia, mucosal lesions, gastroduodenal disease, and ulcers associated with the use of NSAIDs. Ranitidine significantly increases the healing in NSAID-induced gastric and duodenal ulcers both during therapy and after discontinuation of NSAIDs¹⁰. It is also used a prophylactic option for gastroduodenal protection in patients who need long-term treatment with NSAIDs^{11,12}.

Ranitidine has demonstrated good efficacy in the management of gastroduodenal ulcers. A meta-analysis of 293 Randomized Clinical Trials (RCTs) in patients with duodenal ulcers demonstrated higher healing rates at 4 weeks with ranitidine when compared to other H₂ receptor antagonists, antacids, colloidal bismuth, sucralfate, pirenzepine, and prostaglandin analogues. However, superior response was seen with omeprazole¹³.

Ranitidine is an effective treatment for long-term maintenance therapy in duodenal ulcer disease. In a

study in 464 patients with duodenal ulcer disease who received maintenance treatment with either 150 mg/day or 300 mg/day ranitidine for nine years, 95%, 88%, 86%, and 81% were free from symptomatic recurrence of ulcer at 1, 3, 5, and 7 and 9 years, respectively¹⁴. In this study, risk of hemorrhage in patients on maintenance treatment with ranitidine for nine years was less than 2% compared with greater than 12% in untreated patients who were observed for 5 years. In another multicenter study in 160 patients with endoscopically confirmed active duodenal ulcers who received maintenance treatment for six months with either 20 mg/day of famotidine or 150 mg/day of ranitidine, healing of ulcers was maintained in 79% of 58 famotidine-treated patients and in 81% of 52 ranitidine-treated patients¹⁵.

Ranitidine is a preferred option for the long-term treatment of recurrent duodenal ulcer where it helps to reduce the risk of pain and discomfort and lowers the rate of recurrence. Eradication of *Helicobacter pylori* (H pylori) coupled with ulcer healing helps to reduce relapse rates. This is said to be an acceptable and potentially cost saving approach in the management of duodenal ulcers¹⁶. Kurata *et al* reported a higher chance of ulcer recurrence for cimetidine (400 mg HS) when compared to ranitidine (150 mg HS) for use over 12 months in seven clinical trials (OR:1.63; 95% CI: 1.21, 2.21). About 8.4% fewer patients experienced an ulcer recurrence on ranitidine (p<0.01)¹⁷. Continuous use of ranitidine as maintenance treatment in patients with healed duodenal ulcers sustains the healing of ulcers over long term^{18,19}. The two-year GEMUD (Grouped'Etude de la Maladie Ulcéreuse Duodénale) study in 399 patients with duodenal ulcer supported the use of ranitidine (150 mg/day) for maintenance treatment. More patients in the ranitidine arm were free of endoscopic relapse when compared to placebo (83% versus 47%; p <0.0001)¹⁹.

Role in H pylori Infection :

Ranitidine based triple regimens with antibiotics are used in the management of H. pylori infections. Triple regimen of ranitidine bismuth citrate (400 mg bd), amoxicillin (1 g bd), and clarithromycin (500 mg bd) is an effective therapy for the eradication of H pylori in dyspeptic patients. This regimen was found to have comparable eradication rates when compared to lansoprazole-based regimen (65.1% versus 63.6%)²⁰. Mean H pylori eradication rates with 7-day ranitidine-clarithromycin-amoxicillin, ranitidine-clarithromycin-nitroimidazole, and ranitidine-amoxicillin-nitroimidazole are 83%, 86%, and 71%, respectively. Ranitidine and proton pump inhibitor-based regimens show

comparable efficacy for H pylori eradication when they were combined with clarithromycin and amoxicillin (OR: 1.11; 95% CI: 0.88-1.40), or with amoxicillin and metronidazole (OR: 0.92; 95% CI: 0.60-1.41). However, ranitidine based triple regimens show higher cure rates than proton pump inhibitor-based regimens when combined with clarithromycin and a nitroimidazole (OR = 1.65; 95% CI = 1.15-2.37)²¹.

Safety of Ranitidine :

Ranitidine is well tolerated and has a good safety profile with a low incidence of adverse and Serious Adverse Events (SAEs). Overall, the incidence of general side effects at less than 2% is very similar to placebo. The most common adverse events reported with the use of ranitidine include headaches, tiredness, dizziness and mild gastrointestinal disturbance (eg, diarrhoea, constipation and nausea). These complaints rarely call for discontinuation of treatment. Cardiovascular side effects are extremely rare with the use of ranitidine. Some episodes of sinus bradycardia and atrioventricular blockade have been reported with rapid intravenous administration and these resolved with drug discontinuation^{22,23}.

Data from a large population of >26,000 patients in 189 controlled clinical trials (1979 to 1992) along with analyses of post marketing surveillance studies and spontaneously reported adverse events were reviewed to evaluate the safety of ranitidine after more than a decade of use. In this study, >80% patients received up to 300 mg/day dose of ranitidine. The most common organ systems involved in spontaneous Adverse Events (AEs) were central nervous system followed by skin

hypersensitivity reactions, and gastrointestinal system (Fig 1). With prescription doses, the most common individual AEs with ranitidine were headache (3.3%), upper respiratory infections (2.1%), nausea or vomiting (1.8%), abdominal pain (1.7%), diarrhea (1.7%), and dizziness or giddiness (1.3%). SAEs (n=791) which were reported in 445 patient treatments (1.4% of total) with an overall frequency of =1%. There were no significant differences in the frequency of SAEs with ranitidine or placebo (Fig 2)²⁴.

Events have been reported based on estimate of 209 million patient treatments dispensed world-wide after over a decade of use since its launch in 1981.

A small proportion of patients may develop an idiosyncratic reaction shortly after the start of treatment with ranitidine, but continuous, long-term treatment is not associated with any reactions²³. Tachyphylaxis is known to occur after a long-term use of ranitidine and this can develop within 14 days²⁵. However, tolerance to initial dosing with ranitidine is not a progressive phenomenon during continued dosing. A placebo-controlled prospective study in healthy subjects has shown that the antisecretory activity of a maintenance dose of ranitidine (150 mg once daily at night) remains relatively constant between the first and fifth months of continuous dosing²⁶.

The use of proton pump inhibitors over long time warrants vigilance as there is an increased risk of mortality. In a longitudinal observational study in the US Department of Veterans Affairs in new users of proton pump inhibitors (n = 157 625) or H2 blockers (n = 56 842), more deaths were observed in those taking

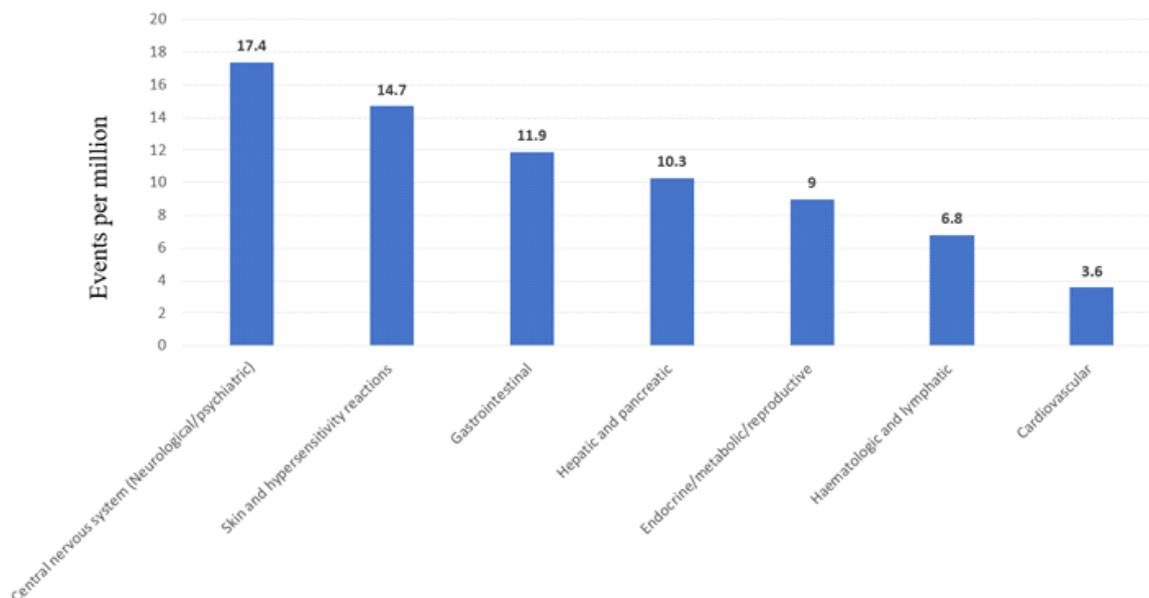


Fig 1 — Organ system review for worldwide spontaneous adverse events with ranitidine use

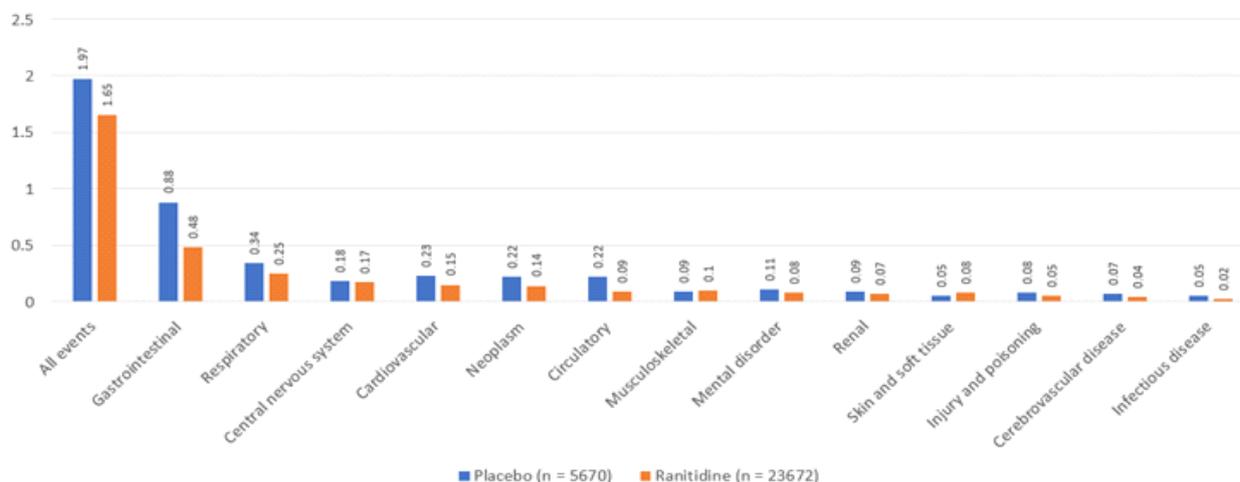


Fig 2 — Incidence of serious adverse events (percentage) with over a decade of use of ranitidine since 1981

proton pump inhibitors than in those taking H2 blockers (37.92% and 35.69%, respectively) over a median duration of follow up of 10 years (interquartile range 6.95–10.00)²⁷. Using big data to emulate a target trial, the authors reported excess mortality due to cardiovascular disease (number of attributable deaths per 1000 PPI Users: 22.91, 95% CI: 11.89 to 33.57), chronic kidney disease (4.74, 95% CI: 1.53 to 8.05), and upper gastrointestinal cancer (3.12, 95% CI: 0.91 to 5.44) in a comparative analysis for the new use of proton pump inhibitors versus H2 blockers on the cause-specific mortality Among patients without documented indication for acid suppression drugs (n = 116 377).

Ranitidine in special populations :

Elderly : Ranitidine is safe for use in the elderly. In a retrospective review of 21 placebo-controlled trials in 4041 patients who received 150 – 300 mg/day dosage of ranitidine for 4 to 52 weeks, no significant differences were seen in the incidence of AEs in elderly (=65 years) or younger (<65 years) patients who received ranitidine or placebo².

Pregnant women : GERD is common in pregnant women and ranitidine has been used for this condition in doses of 150 mg twice daily for 4 weeks. The use of ranitidine during the first trimester of pregnancy is not associated with a major risk of teratogenesis. In a review of data of the United Kingdom General Practice Research Database and the Italian Friuli-Venezia Giulia Health Database (1991–1996), the relative risks for nongenetic congenital malformations associated with the use of cimetidine, omeprazole, and ranitidine were 1.2 (95% confidence interval (CI): 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CI: 0.8, 2.4), respectively,

in first trimester-exposed pregnancies compared with the nonexposed pregnancies²⁸.

The National Birth Defects Prevention Study (NBDPS), a population-based case-control study (4524 cases and 5859 controls from September 1997 to December 2004), evaluated the association of pharmacotherapy for nausea and vomiting in pregnancy with non-cardiac defects in offsprings. The adjusted odds ratios (aOR) of cleft lip with or without cleft palate in offspring exposed to H2 blockers in the first trimester was 0.57 (95% CI: 0.19–1.67). The aOR for cleft palate with H2 blockers, ranitidine, and proton pump inhibitors were 1.04 (95% CI: 0.39–2.75), 1.33 (95% CI: 0.49–3.61), and 2.59 (95% CI: 0.88–7.63), respectively. The aOR for neural tube defects with H2 blockers and ranitidine were 1.80 (95% CI: 0.80–4.05) and 1.28 (95% CI: 0.43–3.82), respectively. In this study, proton pump inhibitors were associated with an increased risk for hypospadias (aOR=4.36, 1.21–15.81) when compared to H2 blockers (aOR: 1.07; 95% CI: 0.41–2.83 and ranitidine (aOR: 0.70; 95% CI: 0.20–2.41)²⁹.

In a prospective study, pregnancy outcomes were compared for 230 pregnant women with gestation H2 blocker use (71% women received ranitidine) and 178 controls who were matched for age, smoking, and alcohol consumption. The most common indications for H2 blocker use were heartburn (415), peptic ulcer disease (30%), epigastric pain (175), and others (12%). There was no increase in major malformations following first trimester exposure to H2 blockers. Major malformations were seen in 2.1% women who took H2 blockers and 3.5% controls³⁰.

Children: Ranitidine has been widely used for various peptic disorders in children and is approved

for the treatment of GERD and healing of erosive esophagitis in children one month or more. It is also available in palatable formulations for administration in infants and children including syrup and effervescent tablets³¹. Ranitidine has been used for the treatment of functional dyspepsia in children³². Further studies are needed to define the efficacy of ranitidine in the long-term management of GERD in children³³.

Risk of carcinoma with use of ranitidine :

In April 2020, the U.S. Food and Drug Administration (FDA) called for an immediate withdrawal of ranitidine from the market. This was due to unacceptable levels of N-Nitrosodimethylamine (NDMA), a probable human carcinogen, in ranitidine medications³⁴. However, more recent evidence does not support this finding. In an in vitro study with simulated gastric fluid with different nitrite concentrations suggested that ranitidine was not converted to NDMA in gastric fluid at physiologic conditions. Ranitidine (1 tablet of 150 mg) was not converted to NDMA until nitrite was 5000 $\mu\text{mol/L}$, a level about 50-fold greater than the upper range of physiologic gastric nitrite concentrations at acidic pH¹⁶. In a recent crossover, RCT in 18 healthy participants, urinary NDMA excretion was compared for oral ranitidine (300 mg) and placebo. The median 24-hour NDMA urinary excretion values for ranitidine and placebo were 0.6 ng (interquartile range [IQR] 0-29.7) and 10.5 ng (IQR 0-17.8), respectively, with a noncured meats diet, and 11.9 ng (IQR 5.6-48.6) and 23.4 ng (IQR 8.6-36.7), respectively, with a cured meats diet.³⁵ This study did not support the conversion of ranitidine to NDMA in healthy adults. Limitations of the study include the study population of healthy adults who may have different gastric pH when compared to patients with acid reflux or ulcers and the administration of ranitidine with breakfast which may impact the saliva sources of nitrites.³⁶ Further, a study published in 2016, reporting an increase in urinary excretion of N-NDMA after ranitidine ingestion was recently retracted in 2021³⁷.

An observational population-based cohort study evaluated the risk of cancer following the use of N-NDMA contaminated ranitidine products in 40,488 ranitidine users (January 2009 – December 2011) from the Health Insurance Review and Assessment (HIRA) database in South Korea³⁸. This study constructed a 4:1 matched cohort of 10122 famotidine users as no NDMA has been detected in famotidine. During a follow up period of seven years, there was no risk of cancer with exposure to NDMA exposure through ranitidine as no statistical difference in the overall cancer risk in

short-term was seen in the ranitidine and famotidine groups (7.45% *versus* 7.56%; HR: 0.99; 95% CI: 0.91–1.07, $p=0.716$).

H2 receptor antagonists are not associated with an increased risk for cancer with long-term use for benign or malignant gastroduodenal conditions. Patients with gastric cancer may present with symptoms similar to benign gastric acid and may receive treatment with H2 receptor antagonists. In a case control study in Italy in patients with newly diagnosed, histologically confirmed gastric cancer ($n=563$) were compared to 150 controls without the malignancy who received either cimetidine or ranitidine. In this study, the risk of gastric cancer was not increased over 5 years or more in these patients though there was an increased risk in the initial few years of initiation of treatment³⁹.

A population-based study in Sweden (2005-2012) compared long term maintenance therapy (defined as at least 180 days during the study period) with proton pump inhibitors and H2 receptor antagonists for the risk of gastric cancer. In this Swedish prescribed Drug Registry, the Standardized incidence ratio (SIR: 3.38, 95% CI: 3.23 to 3.53) for gastric cancer increased by over threefold in 797067 individuals who received proton pump inhibitors for maintenance. When standardized for indications, the risk for gastric cancer was not increased in long-term users of H2 receptor antagonists⁴⁰. In an assessment for the risk of esophageal cancer with the two treatment options, in patients who received maintenance therapy with only histamine-2-receptor antagonists ($n=20177$), there was no increased risk of esophageal adenocarcinoma (SIR: 0.39, 95% CI: 0.04–1.40, $n=2$) or esophageal squamous cell carcinoma (SIR: 0.50, 95% CI: 0.06–1.88, $n=2$)⁴¹.

More recent studies support no association of ranitidine with the risk of cancer.

Yearly incidence of new gastrointestinal malignancies was obtained for 10 years in users of ranitidine, famotidine, and omeprazole from the nationwide database IBM Explorys in the US. This study did not show increased odds of gastrointestinal malignancies with ranitidine compared to famotidine or omeprazole (Fig 3)⁴². In an analysis of the Japan Medical Data Center Claims Database (2005-2018), there was no evidence for an increased risk of cancer with ranitidine or nizatidine compared with cimetidine, famotidine, roxatidine, and lafutidine; the adjusted hazard ratio (ranitidine/nizatidine users vs other H2 blocker users) was 1.02 (0.98-1.07)⁴³. A retrospective, nationwide cohort study (May 1, 1998 to December

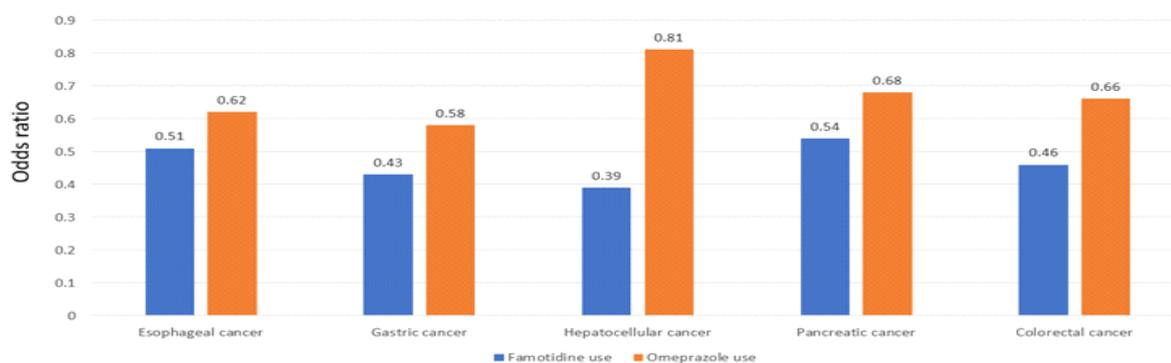


Fig 3 — Risk of gastrointestinal malignancies with use of ranitidine when compared to use of famotidine or omeprazole

31, 2018) in 279,505 patients within the Veterans Health Administration who had a H pylori infection and were prescribed long-term acid suppression demonstrated no association between ranitidine use and future gastric cancer. The users of non-ranitidine H₂ blockers were more likely to develop gastric cancer when compared to the users of ranitidine (HR: 1.83; 95% CI: 1.36-2.48)⁴⁴. In a large prospective nationwide Danish Prescription Registry with 103,565 first time users of ranitidine and 182,497 and 807,725 incident users of other H₂ receptor blockers and proton pump inhibitors, respectively, there was no consistent evidence of increased risk of any upper gastrointestinal cancer following ranitidine use⁴⁵.

Conclusions :

Ranitidine is widely used to reduce gastric acid secretion in conditions like gastric and duodenal ulcers, gastroesophageal reflux, and esophagitis. In these conditions, the use of ranitidine enables a simple approach to treatment with rapid and reliable effect and a safe treatment with reduced risk of recurrence. Ranitidine's safety has been proven for use in children, elderly, and pregnant women. The efficacy and tolerability of ranitidine since its introduction over twenty years ago will ensure its continued use in the treatment of gastroduodenal conditions. Given the recent concerns with ranitidine, clinicians have a choice to discontinue treatment with ranitidine or switch to an alternative therapy based on clinical discretion, patient's conditions, and any apprehensions of the patients or their families for the use of this long-trusted drug⁴⁶.

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Image in Medicine

Bhoomi Angirish¹, Bhavin Jankharia²

Quiz 1

CT scan images of a 45 year old smoker presented with cough since 15 days.

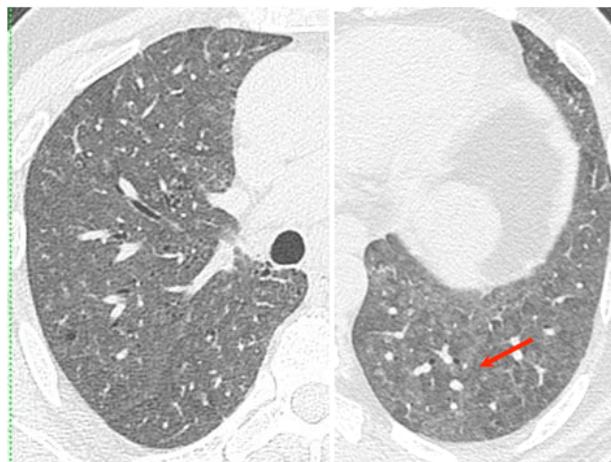
Questions :

- (1) What is the most likely diagnosis in this clinical context?
- (2) What are the common smoking related interstitial lung diseases?
- (3) What are the other differentials of ill-defined bronchocentric nodules?

Answers :

(1) Widespread ill-defined bronchocentric nodules and ground glass opacities are seen diffusely scattered in both the lungs. In the given clinical context, these findings are in favour of respiratory bronchiolitis.

(2) The common smoking related interstitial lung diseases include respiratory bronchiolitis (RB), respiratory bronchiolitis – ILD (RB-ILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell



histiocytosis (PLCH).

(3) The other differentials of ill-defined bronchocentric nodules are acute inflammatory hypersensitivity pneumonitis, inflammatory bronchiolitis, pulmonary infiltrates with eosinophilia and infectious bronchiolitis.

Quiz 2

A 34-year-old man presented with pain in both hip joints since 1 month following high dose oral steroid treatment.

Questions :

- (1) What is the diagnosis?
- (2) What are the stages of avascular necrosis of hip?
- (3) Which is the most sensitive imaging modality to diagnose avascular necrosis?

Answers :

(1) Geographical areas with sclerotic rim are seen in head of femur on either side. Findings are suggestive of avascular necrosis of head of femur.

(2) The Ficat and Arlet classification uses a combination of radiographs and MRI to stage avascular necrosis of the femoral head.

Stage I

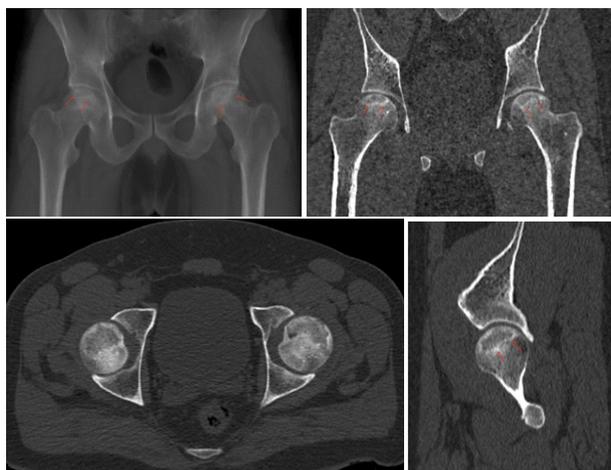
Radiograph : Normal or minor osteopenia.

MRI: Marrow edema.

Stage II

Radiograph: Mixed osteopenia and sclerosis +/- subchondral cysts, without any subchondral lucency.

MRI: geographic defect



Stage III

Radiograph: Crescent sign (subchondral lucency) and eventual cortical collapse.

MRI: Crescent sign, unstable osteochondral fragment, collapse

Stage IV

Radiograph: End stage with secondary degenerative changes.

MRI: same as radiograph

(3) MRI is the most sensitive imaging modality as in early stage, it can well demonstrate marrow edema. It is also more sensitive in identifying subchondral fractures and osteochondral fragments.

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Student's Corner

Become a Sherlock Holmes in ECG

M Chenniappan¹

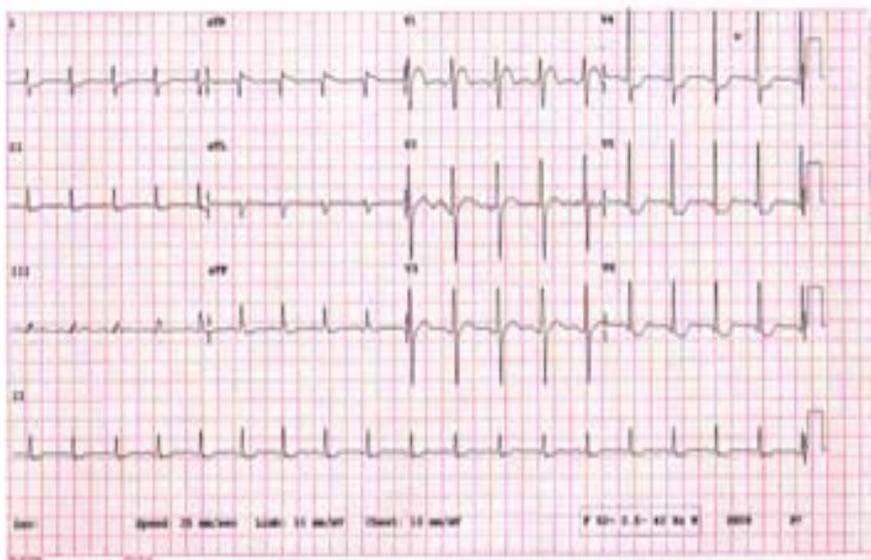
Series 9 :

“Don't Let This ECG Elevation Depress You”

This is the ECG of 52 years old man with chest pain

Questions :

- (1) What is the cause of ST elevation in V1?
- (2) Why is this clue?
- (3) How will you confirm this?
- (4) What are practical implications?



Answers :

(1) It shows ST elevation in V1, mild elevation in V2 and significant ST depression in V5, V6. This is not proximal LAD because ST elevation is regressing from V1-V3 whereas in proximal LAD it will progress. This is not RV MI because there is no Inferior Wall Myocardial Infarction. This is not Brugada as the ST elevation is not classical and there is RBBB pattern. The ST depression in V5 V6 indicates ST vector is travelling away from left sided and towards Right sided leads (ST elevation in V1). The ST depression in V5, V6 (Antero lateral wall) is probably accompanied by ST depression in posterior wall which is shown as ST elevation in V1.

(2) Most often there is reciprocal ST depression in opposite leads due to ST elevation in ST elevation in primary leads. For example, if you have ST elevation in inferior leads due to Inferior Wall Myocardial Infarction, you may have reciprocal ST depression in I, aVL which are superior leads. But in this ECG, primary ST depression of posterior wall is shown as

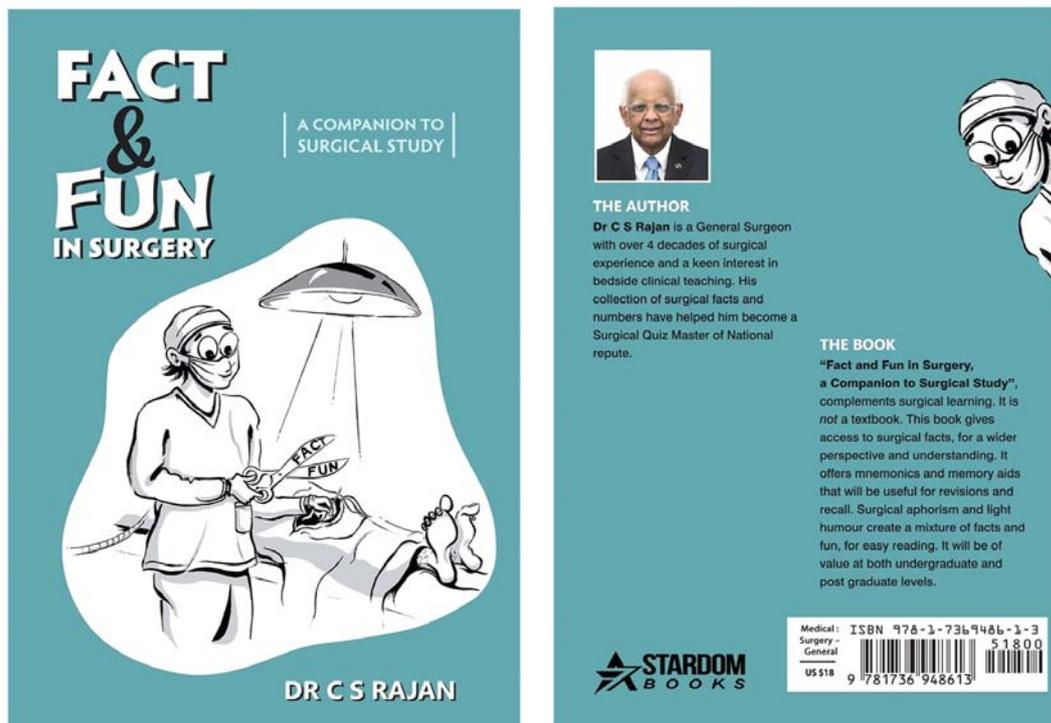
reciprocal ST elevation in V1. So, this is the ECG of rare reciprocal ST elevation. Failing to diagnose this rare reciprocal ST elevation may depress you; that's why this clue.

(3) This first is to flip the ECG and see upside down where you will see significant ST depression in V1 which is actually happening in Posterior wall. The second is to record posterior leads V7, V8, V9 to actually record ST depression there. The third is to see serial ECGs. Here the serial ecgs showed tall R and upright T in V1 indicating evolved PWMI.

(4) The most important question here is to whether to thrombolyse this patient or not. The indication for thrombolysis is for primary ST elevation and not reciprocal ST elevation. Moreover, criteria are to thrombolyse ST elevation more than 2mm in V2, V3 in men and more than 1.5mm in women which are not there in the ECG. But unfortunately, this posterior ST depression has gone for posterior MI. So best option in these types of ECGs will be to have early CAG and suitable revascularization.

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Book Review



Fact & Fun in Surgery, A Companion to Surgical Study by Dr C S Rajan, Publisher : Stardom Books, A Division of Stardom Publishing, 105 – 501 Silverside Road, Wilmington, DE 19809, USA. www.StardomBooks.com Category : Medical : Surgical – General, 1st Edition 2021, Pages 504. Available on Amazon; Price : India -Rs 900/- ; USA \$ 18/-.

WHEN a skillful surgeon, brilliant academician and a versatile surgical Quizmaster decides to share this tremendous surgical wealth, in print with all of us, you get this wonderful compilation. This isn't just another text-book on surgery, it is a companion to surgical study, as clarified by the author. This in effect is the icing to the cake of surgical study. This is not a replacement for the time honored standard surgical text books, it complements the surgical knowledge acquired from those books, as an easy concise surgical reckoner. This is a must-read for all those who want to enjoy the pleasures of reading surgery, by exploring the hitherto uncharted waters of surgical knowledge beyond our mundane text books.

Being an unique "out of the box" concept, you need to open your mind out to it's unique and innovative method of presentation. You will not find your information in the customary anatomical or disease chapters, namely, GIT, Urology, Thyroid etc. Here the plethora of information is presented in a functionally useful manner like mnemonics, definitions, useful clinical information etc. At a glance you have a wide range of surgical signs, relevant clinical scoring systems and classifications, important surgical values, useful surgical anatomy facts etc. It even has some basic information on critical care, radiology and latest surgical technology, all of immense use to the surgeons.

This book endeavors to break the monotony of surgical study, by giving you vital surgical information in a remarkably interesting and wonderfully palatable way. And if you still get bored assimilating that treasure trove of surgical knowledge, then that too has been dealt with, thereby ensuring the desirability of this book; you have a hilarious collection of humour, liberally interspersed amidst the academic fare.

This book is undoubtedly a "must-have" for your surgical books collection. It could actually qualify as an addictively readable non fiction surgical novel.

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Prof of Surgery RGUHS; DNB Examiner,
Co-Author of book 'DECISION MAKING IN SURGICAL ONCOLOGY' Published by Jaypee Bros, 2008

Dr (GpCapt) Deepak Rautray, VSM

Letters to the Editor

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

My CORONA Diary

SIR — By Shri Ram's Grace and all of your blessings, I had beaten the Corona virus.

Let me share some good or bad experiences.

It started one day just as a fever, some 99.7°F, took Paracetamol, and considering it could be corona also, took some other medicines also like Ivermectin, Doxycycline, Vitamin C and Zinc.

I am lucky that by Bhagwan Ganpati's grace, I have good friends in the form of Dr. Ameya Joshi at Borivali, Dr. Aditya Agarwal at Bombay Hospital and Dr. Amit Nabar at SL Raheja Hospital who helped me in every step. I discussed with them, they also suspected Corona, and asked to get tests done, SL Raheja was closest to my home, hence went there, Dr Nabar had arranged for the tests even.

Oof, will never forget the big stick entering into my nose, like duty nurse was playing and enjoying inserting that large stick in the nose that today got opportunity.

So much tickling as well as discomfort but have to bear it. Rapid antigen test turned to be positive. I couldn't believe it at once but had to, the whole world was doomed, I thought of writing my will, but postponed it to next day, was depressed and felt completely lost, as if my world had come to an end.

Dr Nabar told to get admitted, I thought I will bluff him and will run away to a place where no one can find me, but ultimately accepted the fact and came back to the hospital for admission.

Admission process was so smooth, I could never expect. All because of tremendous help by TPA department and admin team. I hadn't faced a single hassle, and was shifted to the ward immediately as soon as I returned back with some luggage.

The only best thing which I did on my own was that I didn't treat myself, rather submitted myself to my treating physicians. I am again lucky that I was treated by best of the teams across the city in the form of Dr. Yatin Gadgil and Dr. Paritosh Baghel. Sometimes I feel pity that all of them had to come for rounds in PPE kit which is extremely uncomfortable, and I wished they could take only online rounds daily so that they are not exposed themselves. Hats off to their dedication.

Fever still there, started Favipiravir, lab reports not good, hence started on Remdesivir. When I heard of Remdesivir, again thought I was a gone case, I informed all my relatives, my close people that what they should do if I don't survive and don't return, ultimately gathered

courage to get the injection. Luckily the ward staff was very much experienced and inserted the iv cannula in a single prick, and that cannula lasted for whole 5 days, no Thrombophlebitis.

However, ward staff didn't left me and took revenge by filling all the thin sample vials with my blood at the first opportunity.

Thanks to all the staff posted in corona ward, they took all the best possible care for me. I will never forget their tender loving care and humane touch

Luckily, improvement started after Remdesivir, otherwise I would also have been in stats now. People would have been talking; He was a good man, though used to speak more, but good at heart.

However, that stage didn't came, and I was discharged in a week, improved and recovered and off medicines now. Thanks again to all my saviors and corona warriors.

Hats off to all of them.

Apologies for writing a long story but not finding more words to thank them all.

PS: 2 doses of Covishield, completed in Jan and Feb.

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Digital Contact Tracing – A Hope in Pandemic Era

SIR — Preceding the declaration of the novel coronavirus pandemic many countries introduced newer strategies and technologies. One such intervention is Contact Tracing (CT) which plays a vital role in this crisis¹. CT is an essential strategy and comprehensive standard public health tool used for many decades to control the spread of different infectious diseases. It serves as a public good and is based on the attempts to identify and trace all contacts regardless who and where they live. Thus CT is important to curb the menace of COVID-19 where the chances of one index person infecting 406 others in 30 days².

According to the recent surveys the success story of the Digital Contact Tracing (DCT) is almost evident since SARS and Ebola. Countries like China, Singapore, South Korea, US, Austria, Spain and UK is evident in providing the advantages of DCT during Pandemic minimizing the disease spread despite the minimal acceptance rate of the CT apps introduced³.

This DCT scaled up the traditional method of contact

tracing which aims at testing, tracing, quarantining or isolating and treating persons to curb the menace created by COVID-19. Initially different contact tracers were involved in CT and calling the contacts of index case became cumbersome. Lack of uniformity and probable different interpretations was responsible for disparity in between the reported and actual scenario. Possibility of information gaps are due to subjective variation⁴.

Now with 4 times increasing caseload, use of social media platforms to collect the information distantly is a preferred method. This CT solution holds the approach to minimise the case overload. The data confidentiality and privacy concerns remain major challenges while opting for digital data management.

Advantages:

- The technology can make the process faster, often without physical intervention and helps to quarantine or isolate the contacts to interrupt the chain of transmission.
- It optimises the manpower and ensures safety of the health workers.
- It allows the contact to provide the accurate information to their health authorities.
- Frequent changing trend and newer added strategies are well implemented via the DCT.
- It even adds up the testing and vaccination status, so that it accurately stratifies the contacts into different risk categories faster than the traditional method of CT.
- It is widely applicable to cover the large number of people during the pandemic⁵.

Disadvantages :

- As per the CDC status, there are very limited data on the performance of this DCT in identifying the true close contacts.
- All individuals cannot participate fully in digital transfer of data questioning digital illiteracy.
- The action is based on the information provided by the contacts.
- Cross questioning and getting exact information may not be possible to withdraw the conclusion and case management.
- Unauthorized access to the forms may compromise the data security and confidentiality.

Conclusion :

- Social mobilization by mass media campaigns are required to spread the awareness and importance of CT among the people need to be intensified.
- National Institute should play proactive role in forming Standard Operating Procedures (SOP) for uniform CT guidelines and disseminate IEC materials time to time throughout the country.

- IT giants can help Government with data management to build public trust and perseverance of the privacy of the contacts during CT.
- Training & utilization of manpower could be strengthened to fill the gap of CT.

Recommendations :

The inter-sectorial co-ordination of the IT field and Health department is a need of an hour for DCT provided with all caveats related to privacy and misuses.

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JIMA, October 2021, Editorial

SIR — Went through your October, 2021 JIMA, Editorial. Nicely written, well researched, one.

We as the Warriors (not only on double sworded and sensitive medical medical stage, but also on hostile politico-other fronts) need to and will stick to : "put your feet in the shoes of the needy sufferers" feeling. It will work in the long run, notwithstanding, the pulls, pushes and pressures.

Highlighting the the R&D problems, particularly in our country, leaders like you and associations like yours' can play a major role - which you laudably do.

I wanted to know as to whether it is lack of funding or of will/knowledge, or both, that is responsible for the disarray !?!

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R Chrungoo

Glimpses of 226th CWC of IMA at Guwahati on 9-10 November, 2021



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(82ND ANNUAL MEETING OF CENTRAL COUNCIL OF IMA)

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The banner includes several images: the IMA logo, a red cross with 'Dr', a collage of Bihar landmarks (Bihar Museum, Patna Museum, Dargah, White Dargah, and a bridge), and a large image of a monument at night.

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