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Contents

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

Editorial

All kudos to the brave hearts...

"There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy. " These lines spoken by Hamlet in Shakespeare's drama Hamlet, to me, will be the ideal line to start the discussion. Truly, in spite of being aware of pandemics playing a "refrain" in the saga of time we preferred to be blissfully confident that nothing of such, of such massive scale, would recur in our lifetime that will not only paralyze the world in a ziffy but would force us to reassess and re-strengthen our shields of defense. Venturing into the hitherto unbound avenues of possible treatments of the disease we have also realized that psychiatry of the health care workers need also to be assessed and analyzed along with their physical health status[1]. Fear psychosis is a major cause of escapism and this is very natural for all human beings be it a patient or a health care worker. The irony of the situation however has a different role to play. While the general public is advised to remain indoors , maintain social distancing, avoid crowd et. al. by instilling in them the element of fear of getting infected, the healthcare workers on the other hand are forced by their ethics of duties to remain in close association with the infected patients and that too under challenging situations where the risk of getting infected is very high. While health workers represent less than 3% of the population in the large majority of countries and less than 2% in almost all low- and middle-income countries, around 14% of COVID-19 cases reported to WHO are among health workers. Although this dichotomy is a necessary evil yet something must be done to protect not only their physical health but also the mental health of the HCWs[2].

There is increasing evidence that suggests that COVID-19 can be *a major* risk factor for stress in HCW. A detailed study was conducted through e-databases, including PubMed, EMBASE, Scopus, and Web of Science (WoS) from December 2019 up to April 12th 2020. All cross- sectional studies published in English assessed the health workers' psychological well-being during the SARS-CoV-2 pandemic. The lowest reported prevalence of anxiety, depression, and stress among HCWs was 24.1%, 12.1%, and 29.8%, respectively. In addition, the highest reported values for the aforementioned parameters were 67.55%, 55.89%, and 62.99%, respectively. Nurses, female workers, front-line health care workers, younger medical staff, and workers in areas with higher infection rates reported more severe degrees of all psychological symptoms[2,3].

Regular screening of medical personnel involved in treating, diagnosing patients with COVID-19 should be done for evaluating stress, depression and anxiety by using multidisciplinary Psychiatry teams. Previous evidence suggested that HCWs were emotionally affected and traumatized during outbreaks, like in the case of severe acute respiratory syndrome (SARS) in 2003[4]. In fact, HCWs during an outbreak might experience the fear of being infected and other unfavorable conditions, such as increasing number of confirmed cases, excessive workload, shortage of personal protective equipment, and intense media scrutiny, that could increase their risk of developing psychological problems. They, therefore, suffered from sleep disorders with worse sleep quality and sleep time reduction aside from anxiety and guilt. An observational cohort study in the United Kingdom and the United States of America indicated that frontline HCWs were 11 times more likely to contract COVID-19 than the general community. Such psychological impact would not only burden HCWs' well-being but might also hinder their ability to effectively manage COVID-19. Their main concern is the risk of transmitting the infection to their families or to acquire it themselves.

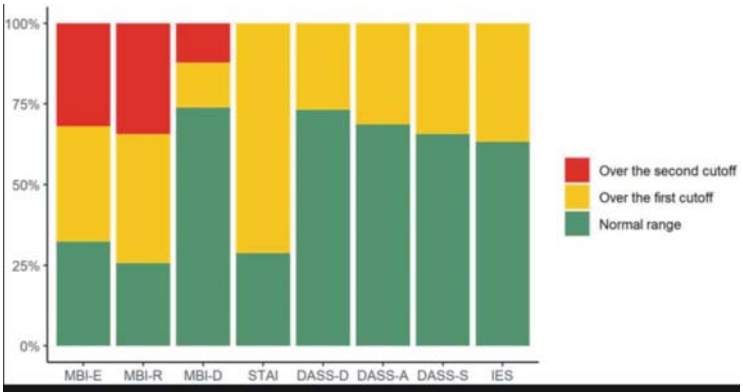

Figure 1 Prevalence of burnout, state anxiety, trait anxiety, depression, stress, and post-traumatic symptoms in health professionals participating to the study. MBI-E, Maslach Burnout Inventory-Emotional Exhaustion; MBI-R, Maslach Burnout Inventory-Reduced personal accomplishment; MBI-D, Maslach Burnout Inventory-Depersonalization; STAI, State-Trait Anxiety Inventory; DASS-D, Depression Anxiety Stress Scales 21-Depression; DASS-A, Depression Anxiety Stress Scales 21-Anxiety; DASS-D, Depression Anxiety Stress Scales 21-Stress; IES, Impact of Event Scale-6.

Ref No 4

Our study demonstrates a significant association between the prevalence of physical symptoms and psychological outcomes among healthcare workers during the COVID-19 outbreak. We postulate that this association may be bi-directional, and that timely psychological interventions for healthcare workers with physical symptoms should be considered once an infection has been excluded. During pandemics, general population have been safeguarded with several precautionary measures including shutdown or slowdown in daily activities, social distancing, reductions in interactions between people, wearing face masks and have good ventilation to reduce the possibility of new infections[5,6]. On the contrary, healthcare professionals were exposed to longer work shifts, in order to manage the growth of health care demand. These critical conditions are exacerbated by the need of wearing personal protective equipment which cause discomfort and difficulties in breathing.

Hereafter I would take the liberty of quoting a major volume of text from the WHO) website that categorically lists the measure to be adopted to protect the covid soldiers[2].

5 steps to improve health worker safety and patient safety

On World Patient Safety Day, WHO reminds governments that they have a legal and moral responsibility to ensure the health, safety and wellbeing of health workers. The Organization's health worker charter calls on all Member States and relevant stakeholders to take steps to:

Establish synergies between health worker safety and patient safety policies and strategies:

Develop linkages between occupational health and safety, patient safety, quality improvement, and infection prevention and control programmes.

Include health and safety skills in personal and patient safety into education and training programmes for health workers at all levels.

Incorporate requirements for health worker and patient safety in health care licensing and accreditation standards.

Integrate staff safety and patient safety incident reporting and learning systems.

Develop integrated metrics of patient safety, health

worker safety and quality of care indicators, and integrate with health information system.

Develop and implement national programmes for occupational health and safety of health workers :

Develop and implement national programmes for occupational health for health workers in line with national occupational health and safety policies.

Review and upgrade, where necessary, national regulations and laws for occupational health and safety to ensure that all health workers have regulatory protection of their health and safety at work.

Appoint responsible officers with authority for occupational health and safety for health workers at both the national and facility levels.

Develop standards, guidelines, and codes of practice on occupational health and safety.

Strengthen intersectoral collaboration on health worker and patient safety, with appropriate worker and management representation, including gender, diversity and all occupational groups.

Protect health workers from violence in the workplace

Adopt and implement in accordance with national law, relevant policies and mechanisms to prevent and eliminate violence in the health sector.

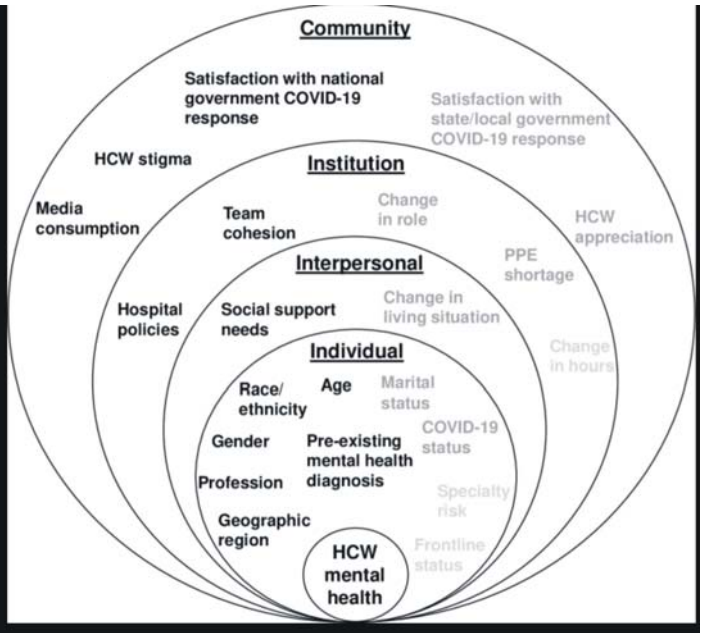

Fig 1. Socio-ecological model for mental health outcomes among healthcare workers during the COVID-19 pandemic. Socio-ecological factors in light grey text were not significantly associated with any mental health outcome in unadjusted and adjusted models.

Ref No 6

Promote a culture of zero tolerance to violence against health workers

Review labour laws and other legislation, and where appropriate the introduction of specific legislation, to prevent violence against health workers.

Ensure that policies and regulations are implemented effectively to prevent violence and protect health workers.

Establish relevant implementation mechanisms, such ombudspersons and helplines to enable free and confidential reporting and support for any health worker facing violence.

Improve mental health and psychological well-being

Establish policies to ensure appropriate and fair duration of deployments, working hours, rest break and minimizing the administrative burden on health workers.

Define and maintain appropriate safe staffing levels within health care facilities.

Provide insurance coverage for work-related risk, especially those working in high-risk areas.

Establish a 'blame-free' and just working culture through open communication and including legal and administrative protection from punitive action on reporting adverse safety events.

Provide access to mental well-being and social support services for health workers, including advice on work-life balance and risk assessment and mitigation.

Protect health workers from physical and biological hazards.

Ensure the implementation of minimum patient safety, infection prevention and control, and occupational safety standards in all health care facilities across the health system.

Ensure availability of personal protective equipment (PPE) at all times, as relevant to the roles and tasks performed, in adequate quantity and appropriate fit and of acceptable quality. Ensure an adequate, locally held, buffer stock of PPE. Ensure adequate training on the appropriate use of PPE and safety precautions.

Ensure adequate environmental services such as water, sanitation and hygiene, disinfection and adequate ventilation at all health care facilities.

Ensure vaccination of all health workers at risk against all vaccine-preventable infections, including Hepatitis B and seasonal influenza, in accordance with the national immunization policy, and in the context of emergency response, priority access for health workers to newly licensed and available vaccines.

Provide adequate resources to prevent health workers from injuries, and harmful exposure to chemicals and radiations; provide functioning and ergonomically designed equipment and work stations to minimize musculoskeletal injuries and falls.

In addition to the Health Worker Safety Charter, WHO has also outlined specific World Patient Safety Day 2020 Goals for health care leaders to invest in, measure, and improve health worker safety over the next year. The goals are intended for health care facilities to address five areas: preventing sharps injuries; reducing work-related stress and burnout; improving the use of personal protective equipment; promoting zero tolerance to violence against health workers, and reporting and analyzing serious safety related incidents.

India's deadly second wave of Covid-19 has claimed the lives of almost 270 doctors. In the first wave of the pandemic in 2020, nearly 750 doctors had succumbed to the disease.

In September last year, the IMA had demanded that the Indian government treat doctors who succumbed to Covid-19 as martyrs. The IMA said that it would help the families of the deceased to be eligible for the right compensation. "…Their families and children deserve solace and from the government. IMA also urges the government to seek data from the representatives of nurses and other healthcare workers," National President, IMA Dr Rajan Sharma wrote to the Government of India in September 2020[7]. There are many slips between the cup and the lips and there are many promises which are made but not implemented. How many doctors who have sacrificed their lives have received proper compensation? Has the Government as well as the private health sector strictly adhered to Health Worker Safety Charter recommended by WHO? While even the workers in factories are protected by the Factory Act laid down in the laws of the land why not these brave-hearts be protected and allowed to live when they themselves present a fresh lease of life to their patients. It is high time that the health workers together with the citizens of India raise their voice in unison to demand health and safety as their primary right.

Offence is the best form of Defense and to defend we need brave warriors who can outbrave the alien forces. We thus require a regiment of strong and healthy warriors. Undeniably our HCW are our defenders and we must avail for them a strong support system so that they can invest all their skills to fight the Lucifer called COVID 19.

"Asato ma sadgamaya tamaso ma jyotirgamaya".

Let us be lead from the path of untruth to the avenue of truth/ Lead us be lead out of the tunnel of darkness to the zone of halo and light. All kudos to the brave hearts.

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Original Article

A Study from Eastern India on the Role of Dapsone Therapy in Patients of Persistent and Chronic Immune Thrombocytopenia; Where Do We Stand ?

S Karthika[1], Prakas Kumar Mandal[2], Shuvraneel Baul[3], Tuphan Kanti Dolai[4]

Background : Immune thrombocytopenia (ITP) is a heterogeneous disorder and remains a diagnosis of exclusion of other causes of thrombocytopenia. Even though response to first line therapy is around 75-80%, almost 60-70% of adult patients experience relapse. Dapsone, first described as potential therapeutic agent for ITP since 1988, with a response of 29-63%.

Material and Method: This Prospective interventional study was conducted on 50 persistent and chronic ITP patients. Dapsone was given orally at a dose of 2mg/kg/day; followed up for 12 months. Response evaluated as per published guidelines.

Result : Out of total 50 patients, 36(72%) were female. Patients with persistent and chronic ITP were 15(30%) and 35(70%) respectively. Non-responders were withdrawn from the study at the end of 6 months. At the end of 12 months, complete response found in 10(20.8%) patients.

Conclusion : It is a very cheap drug; evaluation of its role in safety and efficacy help us to reduce the treatment burden in developing countries like India. No predictors of response were found. The major difference in the response in our study compared to previous studies need to be clarified further with large sample size.

[*J Indian Med Assoc* 2021; **119(6):** 16-21]

Key words **: Immune Thrombocytopenia, Persistent And Chronic, Dapsone Therapy, Response.**

The incidence of ITP is 0.2-0.4 new cases per 10,000/year in adults and 0.2-0.7 per 10,000/year in children and can be an isolated primary condition or it may be secondary to other conditions[1,2]. Out of all, 80% are primary ITP. Likelihood of spontaneous remission from ITP is age related, with 1-year remission rates of, 74% in children from 1 year of age, 67% in those between 1 to 6 years and 62% in 10 to 20 years of age[3]. Natural history data in adults are less well studied, with reports of 20% to 45% of patients achieving complete remission by 6 months[4]. Sustained response to steroids, intravenous Immunoglobulin (IVIg) and anti-D noted in approximately two third of patients. Rituximab used as second line therapy, shown response rate of 40%. Thrombopoeitin Receptor agonists have well established efficacy and safety; but these are very costly and risk of infection is high. Splenectomy is curative for chronic ITP with a response rate of 66-88%; relapse rate of 15%. But not preferred due to risk of surgery, thrombosis and infection.

Editor's Comment :

- Diagnosis of Immune thrombocytopenia (ITP) remains a diagnosis of exclusion of other causes of thrombocytopenia.
- Though response to first line therapy is around 75-80%, almost 60-70% of adult patients experience relapse.
- Dapsone used in chronic and persistent ITP with reported response rate of 29-63%, is a very cheap drug.
- Evaluation of its role in efficacy and safety help us to reduce the cost of treatment burden in resource constraint countries like India.

Dapsone is used in ITP at an oral dose of 1–2 mg/kg daily; rapidly and completely absorbed with peak drug levels being achieved within 4-8 hours of intake. Excretion of the drug is mainly through urine and a constant blood level can be maintained with regular daily dosing. The elimination half-life is estimated to be 30 hours[5,6]. There is no clear explanation of how it helps in the treatment of ITP, although some argue that excessive red cell destruction by Dapsone blocks the reticuloendothelial system[6]. However, in many patients treated with Dapsone, there is no significant drop in hemoglobin levels, and some remain in remission even after the drug is discontinued[7]. It is well tolerated drug, with minimal adverse effects mentioned in literature. It causes hemolysis in patients

Department of Hematology, NRS Medical College & Hospital, Kolkata 700014

[1]DM (Clinical Hematology), Post Doctoral Trainee

[2]DM (Clinical Hematology), Associate Professor and Corresponding Author

[3]DM (Clinical Hematology), Assistant Professor

[4]DM (Clinical Hematology), Professor & Head

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with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency; thus mandatory to check G6PD assay before starting Dapsone. There are cases of hemolysis noted in patients with normal G6PD assay. Cases of itching, Steven Johnson Syndrome and also hepatitis noted in few studies[7].

Materials and Methods

This was a prospective interventional study conducted over a period of two years from January, 2018 to December, 2019. Patients aged between ≥3 years to ≤60 years with features of bleeding manifestation were included in the study after getting informed consent and diagnosed as persistent and chronic ITP as per American Society of Hematology (ASH) 2011 guideline[8,9]. Patients aged >18 years were considered as adults those with age ≤18 years as children (age corrected to the nearest whole number). A detailed history was taken along with clinical evaluation of all the patients. Clinical history and physical examination was done in all patients meticulously. The severity of bleeding graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)[10].

Inclusion criteria:

Patients included in the study fulfilled all the following criteria-

(a) age ≥3 years to ≤60 years,

(b) Diagnosed case of Persistent and Chronic ITP,

(c) Platelet count<30×10^9/L or,

(d) Platelet count <50×10^9/L with bleeding manifestation.

Exclusion criteria :

(a) Patients with secondary ITP patients, pregnant patient or lactating mother,

(b) Earlier treated with splenectomy, with active severe infection or history of severe infection within 4 weeks before inclusion,

(c) Patients who are allergic to sulfonamides, patients with history of methemoglobinemia, G6PD deficiency (screening done by methemoglobin reduction test in both sexes),

(d) Patients with hemoglobin level<8.0 gm/dl and/or neutrophil count<1.5x10^9/L,

(e) Patients with history of autoimmune or hereditary haemolytic anemia

(f) And, patients with impaired liver or kidney function.

Rescue medications (dose increment of steroid or IVIg) required in 21 patients. Patients were on various dosage of steroid, tapering was started from 8 weeks after addition of Dapsone. Gradual tapering of steroid was done over a period of 8 weeks. Complete Blood Count (CBC), Liver Function Test (LFT), urea, creatinine were assessed periodically.

Response evaluation: Responses were assessed as per "ASH-2011 Evidence based practice guidelines for ITP"[9]:-

- ***Complete response :*** Platelet count of 100×10^9/L or more, measured on two occasions, 7 days apart and the absence of bleeding without rescue medication.
- ***Response :*** Defined as platelet count of 30×10^9/L or more and at least a doubling of baseline platelet count measured on two occasions, 7 days apart.
- ***No response :*** Less than 30 × 10^9/L or less than 2 fold increase in the platelet count or with bleeding manifestation. Measured on more than one occasion, one day apart.

Criteria used for non-responders: Platelet count at the end of the study is <30 x 10^9/L, but also, during the study period if:

- They need a rescue therapy, 6 weeks after inclusion.

or

- They receive any other second line therapy.

Patients not responded even after 6 months (this time period was taken as our patients were on overlapping steroid for 16 weeks), were withdrawn from study, and treated with other therapeutic modalities.

Statistical Analysis: Quantitative values were reported as median (1st-3rd interquartile) and qualitative data as percentage. P-values were derived using Chi square test and Mann-Whitney test for qualitative and quantitative values, respectively. Wilcoxon matched pairs test was used to compare platelet count before and after treatments. $P<0.05$ was considered significant. Statistical analyses were performed with STATATM Software (Stata Corp).

Results

Out of 50 patients, 36(72%) were female. Median age was 20 years (range,3-60 years). These included 26(52%) children≤18 years and 24(48%) adults >18 years. Fifteen(30%) patients diagnosed as persistent ITP and 35(70%) has chronic ITP. All the patients were treated with steroid and IVIg previously. Duration of symptoms before starting dapsone was 4-32 months. Twenty four(48%) patients had grade1, 22(44%) patients had grade 2 and four(8%) had grade3 bleeding manifestation as per NCI-CTCAE criteria.10 There was petechiae and purpuric spots in 45(90%) patients, wet purpura in 21(42%) patients, epistaxis in 21(42%) patients, menorrhagia in 13(26%) patients and gum bleed in 11(22%) patients. The median platelet count

of total cases at diagnosis was 13x109/L (2-20x109/L) in both adults and children. Summary of the cohort (n=50) represented by CONSORT flow diagram in Fig 1. Two patients were withdrawn from study at the beginning (one due to itching with rashes, other patient due to severe bleeding requiring other mode of therapy).

Disease duration prior to Dapsone ranges from 4-32 months. Unable to afford for costly medicines and various complications with splenectomy, patients were continued with steroid in various doses. Steroid was continued till 8 weeks, and gradual tapering was done. Dapsone was administered at the dose of 2 mg/kg/day, responses evaluated periodically. As shown in Fig 2, response at 2 months was 72.9%, while the patient was on steroid. After omission of steroid, response rate reduced to 37.5% at the end of 6 months. At the end of 12 months only 10 (20.8%) patients were maintaining the platelet count.

Out of 36 female patients, ORR noted in 8 (22%) patients and out of 14 male patients ORR noted in 2 (14%) patients. Subgroup analysis of patients (n=15) with persistent ITP, ORR noted in 4 (27%) patients; response in 3 (20%) patients, CR noted in 1 (7%) patients. Patients (n=33) with chronic ITP, ORR noted in 6 (18%) patients; response in 5 (15%) patients, CR in 1(3%) patient. Subgroup analysis of response in children (n=25) ORR in 8 (32%) patients, out of which CR noted in 6 (24%) patients. Adult (n=23) cohort showed, ORR in 2 (8.7%) patients, none of the patients in CR.

Most patients (n=46) tolerated the therapy well. As shown in Fig 3, severe side effects noted in two patients; intractable itching with rashes in one patient and fall in hemoglobin (2.4 gm/dl) noted in other patient. Mild to moderate adverse effects seen in 46% patients; 10% patients complained of nausea, symptoms subsided with oral antiemetic and lifestyle modification. None of the patient warrants dose modification. Six percent patients were complaining of mild itching. Headache was seen in 7% patients, relieved with analgesics. Deranged LFT (less than 3 fold increments in AST/ALT) found in 13% patients, therapy continued with weekly once follow up. Significant fall in hemoglobin (>1.0gm/dl) noted in 6 patients. Out of 10 responded patients, fall in Hb (>1.0gm/dl) noted in only three patients.

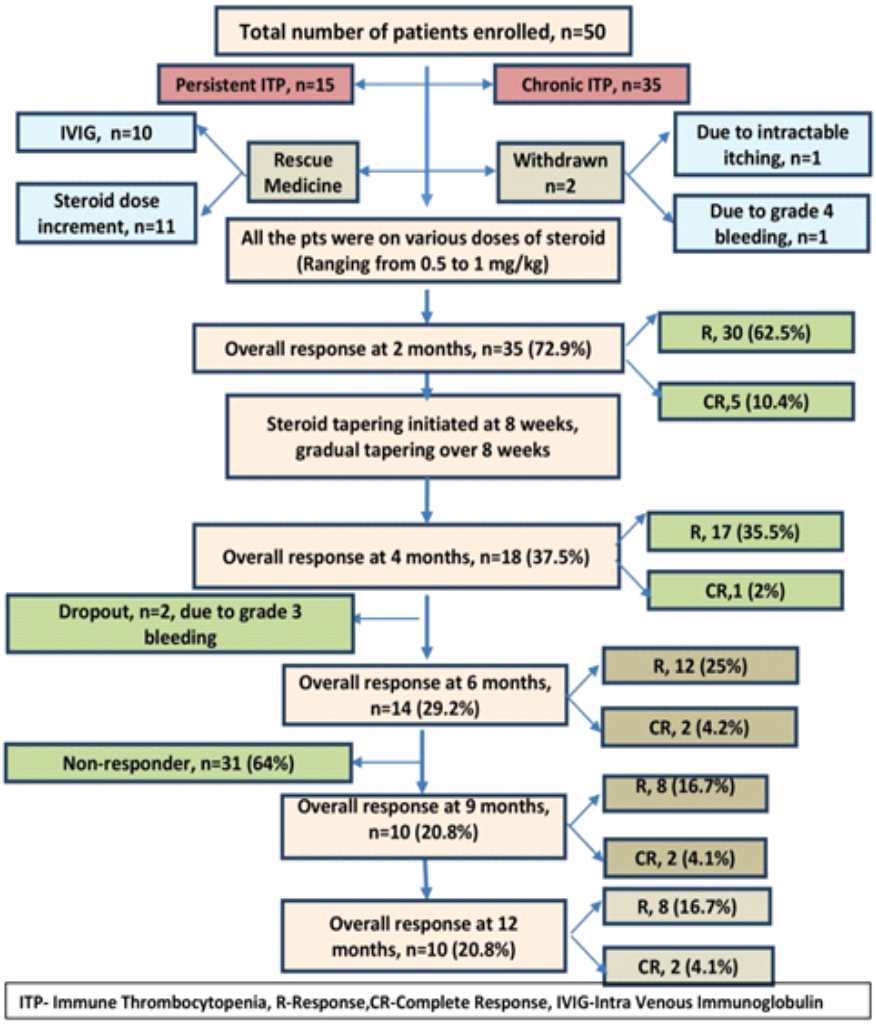

Fig 1 — The CONSORT flow Diagram of the cohort included in the study (n=50)

Discussion

In contrast to published literature[2,3,4], in the present study, pediatric population is high, possibly due to more number of younger populations in India, and also it may be due to the fact that in younger population there is a chance of getting more medical attention than elder population in developing countries like India. Response rate is better in pediatric population, but there is no statistical difference (p=0.103)

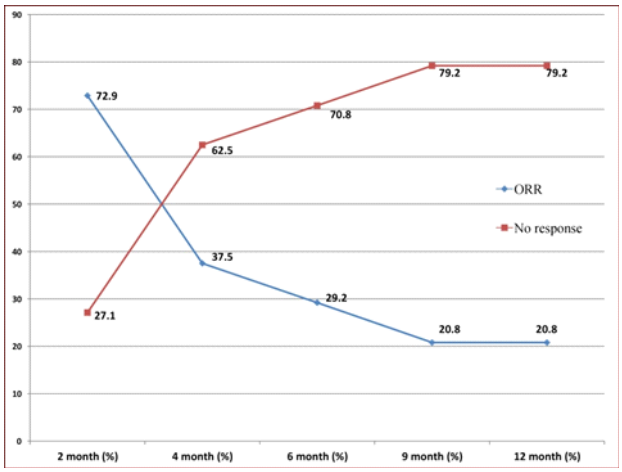

Fig 2 — Comparing response at various time points in total cohort

matching the literature.

In the present study, female population was more (72%) in all age groups. An association between female gender and increased risk of chronic ITP was found in majority of studies[4,7,11]. However some of the studies on childhood ITP reported a slightly higher preponderance in boys,[11-13] while others found an equal age distribution[14]. At the end of 12 months, no statistical difference in response noted as per gender (p=0.81). As per phase of ITP, Dapsone response, no statistical difference were found between the persistent and chronic ITP patients (p=0.70).

Duration of disease at the time of entry into the study ranges from 4 to 32 months and most of the patients were on various doses of steroid. Khan YB et al15 from Jammu and Kashmir, India also conducted a similar study in 100 ITP patients, mean interval between diagnosis and start of Dapsone was 2 years

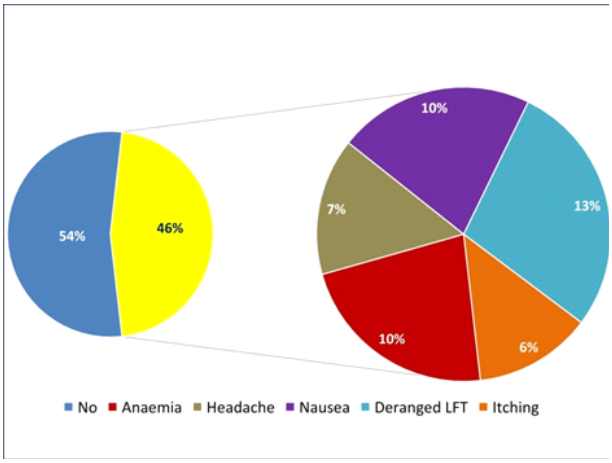

Fig 3 — Side effects profile with Dapsone therapy [includes mild and moderate adverse effects noted in 46% of the study population. Severe adverse effects found only in two (4%) patients]

similar to present study. Duration of disease doesn't have any effect on therapy response. Platelet at diagnosis was not found to have any impact in response outcome.

Response at the end of two months was noted in 35 (72.9%) patients, at this point of time patients were on both steroid and Dapsone. In the study by Khan YB *et al*[15], the mean time to onset of response was 21 days (range, 8 - 97). Maximum response was noted at two months in our cohort. But the exact time of action could not be assessed because patients were on Dapsone and overlapping steroid. This combination was continued for two months, because most of the studies had shown variable response duration ranging from 9-260 days. Most of the studies were done as Dapsone monotherapy without steroid overlapping except one such published in the year 2017 by Cle´mentine E *et al*[16] In the said study[16], patients received prednisone at a median dose of 1 mg/kg/day and was discontinued after a median duration of 28 days (21–37.5). Response is better in patients with steroid and Dapsone compared to Dapsone monotherapy. Steroid sparing effect of dapsone is proven in Leprosy, but not in ITP. This role of Dapsone has to be evaluated further in large trail. In future that may help us to reduce the side effects of prolonged, high dose use of steroid.

At the end of 6 months, we found that overall response maintained in only 14 (29.2%) patients, out of which response noted in 12 (25%), complete response noted in 2 (4.2%) patients. At the end of 9 months another 4 patients had shown loss of response with relapse of disease. This response is maintained at the end of 12 months. ORR at the end of 12 months were 20.8%, compared to other studies (as shown in Table 1) the response rate was very less. All our patients were having good compliance to therapy and on regular follow up; still very low level of response as compared to others which we can't explain.

In the reports by Cle´mentine E *et al*[16] steroid given over a period of 28 days; then tapered suddenly; response noted with Dapsone monotherapy in 47.4%(n= 9/19 patients) with a CR of 21.1%(n=4/19) and a PR in 26.3%(n=5/19). But, in the present study, even after slow tapering of steroid over 4 weeks, response to dapsone was poor. Almost 78% of patients at the end of 6 months required other treatment modalities to manage the bleeding manifestation.

In the present study, patients achieved response in 8 (16.7%) patients, compared to CR only in 2 (4.1%). Study by Patel AP *et al*[17] using an average dose of dapsone of 1.57 mg/kg/day showed mean time

Table 1 — *Comparison of the results from present study with different other studies*

Parameters	Godeau *et al*[20]	Damodar *et al*[7]	Vancine-Califani *et al*[21]	Zaja F *et al*[18]	Patel AP *et al*[17]	Khan YB *et al*[15]	Clementine E *et al*[16]	Present study
Year of study	1993	2005	2008	2012	2014	2014	2017	2019
Type of study	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Prospective
No of patients	66	90	52	20	38	100	42	50
Median age (years)	48	20.6(3-61)	38(13-78)	51(27-74)	29.5(20-68)	36	57.1(34-77)	20(3-60)
Median platelet count before Dapsone 10^9/L	NA	13.2	NA	19	12	8000	14(6-22)	13
Complete response/ response	NA/50%	48.9/63.3%+	NA/44.2%	20%/55%	40.5%/48.5%	NA/47.7%	38.1%/16.7%	4.1%/ 16.7%
Time to response in days	21(8-90)	105(30-270)	-	30(15-60)	59(27-108)	21(8-97)	29(24-41)	-
Relapse during Dapsone therapy	1/20(5%)	NA	NA	0	2/18(11.1%)	0	6/23(26.1%)	38/50(76%)
Withdrawal due to toxicity n(%)	7/66 (10.6)	3/90 (3.3)	1/52(1.9)	1/20(5)	2/38(5.3)	0	9/42 (21.4)	1/50(2%)
Average dose	75-100 mg/day	2.15 mg/kg/day	100 mg/day	50-100 mg/day	1.57 mg/kg/day	1-2 mg/kg/day	33.3-100 mg/day	2 mg/kg/day
Average treatment duration in responders (m)	12.5	9 (PR)-12.5(CR)	9.7	31	10	5 years	9.7	12

NA = not available, y = years, m = months

to response of 57 days (range, 19-108 days). The response rate was 48.6% (complete response = 40.5%). They concluded that, response to dapsone is slow, sustained, and relapses are uncommon on therapy but, it's withdrawal leads to relapse in most cases. Damodar S *et al*[7] observed response rate of 63.3% (CR in 48.9%). Zaja F *et al*[18] reported response in 55% cases with CR of 20%. They used Dapsone at a lower dose (100mg OD, average weight: 77kg, range: 57–100kg) in comparison to the present study (2mg/ Kg/Day) and Dapsone was discontinued if there was no response after two months.

The major difference in the response in our study compared to other studies need to be clarified further with large sample size. Study by Patel AP *et al*[17] had shown that time to response and peak response was noted in 57 days and 155 days respectively. This study highlighted the very late cumulative response with Dapsone. The non-responder patients in the present study were withdrawing from the study at the end of 6 months. It needs to be studied further to prove whether prolonging therapy beyond this period have any effect in increasing response to the therapy.

In a very recently published review article by Matzdorff A *et al*[19] have shown that, therapeutic response may be slow and an effect is usually to be expected after 4-6 weeks but have well established safety profile. There was no significant difference in the mean fall in haemoglobin level between responders and non-responders 1.0gm/dl (range, 0.4–2.0) *versus* 1.8gm/dl (0.9–2.5) respectively (p=0.16). This gives an idea that mechanism of action of Dapsone, may not due to the destruction of Red Blood Cells (RBCs) in reticuloendothelial system and sparing platelets. The major difference in the response in our study compared to other studies need to be clarified further with large sample size.

Limitations of the study:

- Small sample size
- Shorter period of study including follow up
- Long term adverse effects could not be studied

Conclusion

At the end of 12 months, only 20.8% patients were maintaining the platelet count. Though dapsone is cheap, safe and well tolerated drug in all age group of patients but, it's long term response rate (especially complete remission, 4.1%) is not encouraging and relapse is substantial.

Ethics approval : The study was approved by the institutional ethical committee

Source of Funding : None

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Original Article

Orientia tsutsugamushi — A Leading Cause of AES in West Bengal, India

Partha Sarathi Saha[1], Rinku Chakraborti[2], Aparna Chowdhury[3], Shubhra Chattopadhyay[4], Saiantani Mondal[5], Bishal Gupta[6], Bibhuti Saha[7], Bhaswati Bandyopadhyay[8]

Introduction : Acute Encephalitis Syndrome (AES) is a major public health problem in West Bengal, India including West Bengal. Japanese encephalitis virus accounts for < 10% of AES cases, while the etiology of remaining cases is still largely unknown. Scrub typhus is known to cause AES but no data exists regarding the proportion of AES cases due to scrub typhus in the state of West Bengal.

Aims : The study was aimed at identifying the proportion of *Orientia tsutsugamushi* infection among the patients presenting with AES and to analyze the associated demographic characteristics, clinical profile and laboratory parameters.

Methods and Material : Serum samples of 430 suspected AES cases were collected from different hospitals of Kolkata and MAC ELISA was performed at referral virology laboratory of School of Tropical Medicine, Kolkata over the period, April 2018 to March 2019.

Results : 133 (30.93%) out of 430 suspected AES cases were found reactive for scrub typhus IgM. Most of the cases were reported during the monsoon and post-monsoon period and under-15 children were commonly affected.

Conclusions : In this study 30.93% of AES cases were positive for scrub typhus. So it needs to be included in the differential diagnosis of AES in West Bengal.

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***Key words* : Acute Encephalitis Syndrome, *Orientia tsutsugamushi,* MAC ELISA, West Bengal.**

Acute Encephalitis Syndrome (AES) is a major public health problem in West Bengal, India.

Traditionally Japanese encephalitis (JE) has been considered to be the most important cause of AES in our country[1]. The first major outbreak of JE occurred in 1973 in Bankura and Burdwan Districts of West Bengal with subsequent outbreak occurred in 1976[2].

The State Health Department of Government of West Bengal undertook mass vaccination program against JE in several endemic districts using live attenuated JE vaccine SA-14-14-2[3]. As a result incidence of JE was grossly reduced in the Southern Districts of West Bengal from 22.76% in 2011 to 5% in 2012[3]. Although JE cases have declined AES cases are on the rise[3]. Hence focus has been shifted to identification of treatable, Non- JE etiologies of AES cases. Scrub typhus caused by *O tsutsugamushi* is a re-emerging disease in India and is known to cause Acute Encephalitis Syndrome. Several studies on AES from Assam, Uttarpradesh and Bihar revealed that scrub typhus is a major cause of AES in those states[4-6]. No data exists regarding the proportion of scrub typhus AES cases in West Bengal. Hence, this study was undertaken to investigate the etiology of *O tsutsugamushi* in AES cases and to determine its associated epidemiological, clinical and laboratory parameters.

Editor's Comment :

- Unlike Japanese Encephalitis, Scrub typhus Acute Encephalitis Syndrome is curable if diagnosed and treated early. So, Scrub typhus IgM ELISA should be considered mandatory in every patient presenting with AES to avoid undue complications and mortality.

Materials and Methods

430 suspected AES cases of all age groups, admitted in different hospitals of West Bengal, whose serum samples were referred to the Virology Unit of School of Tropical Medicine, Kolkata during the period April, 2018 to March, 2019 were included in the study.

Hemolysed serum samples, inadequate samples, improperly labelled samples and samples where proper clinical information was lacking were excluded from the study.

Department Microbiology, Calcutta School of Tropical Medicine, Kolkata 700073
[1]MD, Postgraduate Trainee
[2]MD, Medical Officer
[3]MSc, Molecular Biologist
[4]MD (Microbiology), Senior Resident
[5]M Tech, Senior Resident
[6]MD (Microbiology), Senior Resident and Corresponding Author
[7]MD, Professor, Tropical Medicine
[8]MD (Microbiology), Professor

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Serum samples were stored at 4°C in the refrigerator and tested within 24-48 hours. The study protocol was reviewed and approved by the Institutional Clinical Research and Ethics Committee.

IgM antibody capture (MAC) ELISA was performed by In Bios international Inc Scrub Typhus Detect™ IgM ELISA system. The samples were tested strictly following the manufacturer's protocol. The cut-off OD value in India is 0.5[7].

Observations

During the one year study period (April 2018 to March, 2019) total 430 serum samples were selected as per the inclusion criteria among which 133 (30.93%) samples tested positive for scrub typhus IgM with slight female preponderance (Female- 68 ie, 51.12%).

Though all age groups were found to be affected, highest no of cases [90 cases out of 133 seropositive ie, 67.67%] were reported from under-15 age group.

Month wise distribution showed that the maximum number of cases of scrub typhus AES were found during monsoon and post monsoon period (August, September, October, November) while least or no cases were detected during the month of January, February and March (Fig 1).

As the study was conducted in Kolkata, most of the positive cases were from the adjoining rural Districts like South 24 Parganas, North 24 Parganas and Howrah. Few cases were reported from the metropolitan City of Kolkata.

Most common symptoms were fever (100%), headache (82.70%), bodyache/myalgia (78.19%) followed by convulsion (77.44%), altered sensorium (74.44%), nausea and vomiting (50.38%), lymphadenopathy (48.12%), skin rash (36.09%) and cough with/without shortness of breathing (32.33%). Both convulsion and altered sensorium was noticed among 70 (52.63%) patients (Table 1).

92(69.17%) out of 133 scrub typhus IgM seropositive AES cases had H/O fever for more than 7 days duration which indicates that AES develops more in the later course of the disease when fever remains undiagnosed for prolonged periods. The longest duration of fever recorded was 2 months.

Table 1 — *Age distribution of scrub typhus AES cases (n=133)*

Age- group	Reactive cases (n=133)	Percentage (%)
0 - 15	90	67.67
16-30	22	16.54
31 - 45	9	6.77
46 - 60	4	3.00
>60	8	6.02

Characteristic eschar was detected only in 27.07% cases while 25.56% patients presented with positive meningeal signs. Hemiparesis was noticed in two patients (Table 2).

Table 2 — *Signs and symptoms of scrub typhus AES cases*

Signs and symptoms	No of cases	Percentage
Fever	133	100.00
Headache	110	82.70
Bodyache / Myalgia	104	78.19
Convulsion	103	77.44
Altered Sensorium	99	74.44
Both Convulsion & Altered Sensorium	70	52.63
Nausea & vomiting	67	50.38
Lymphadenopathy	64	48.12
Skin rash	48	36.09
Cough & respiratory distress	43	32.33
Eschar	36	27.07
Abdominal pain	23	17.29
Meningeal signs	34	25.56
Hemiparesis	2	1.50
Pedal edema	1	0.75

Out of the 133 scrub typhus IgM reactive cases 68 (51.12%) had haemoglobin levels (9-12) gm/dl whereas 57(42.86%) cases had hemoglobin levels less than 9gm/dl. Leucocyte count was found to be in the normal range (4000-11000/cmm) in 56 (42.11%) cases. About 57.14% cases presented with leucocytosis (>11000/cmm) and most of them had a history of fever of >7 days duration. Thrombocytopenia (50,000—100000/cmm) was quite a common feature and detected in 31.58% but levels below 50,000 was rarely observed. Seum

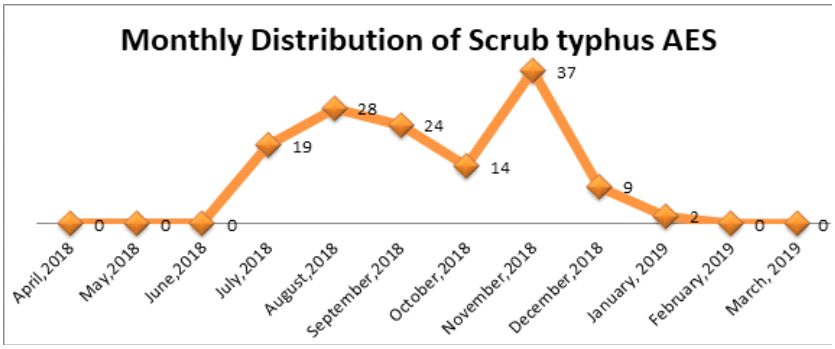

Fig 1 — Monthly distribution of scrub typhus AES cases

bilirubin level was elevated in 65 (48.86%) cases but rarely exceeded 3 mg%. Raised serum creatinine level (>1.5mg%) was noticed among 20 (15.04%) cases (Table 3).

Table 3 — *Laboratory parameters of scrub typhus AES cases*

Laboratory parameters	No of cases	Percentage
Hemoglobin levels :		
<9 gm%	57	42.86
9-12 gm%	68	51.12
12-14gm%	8	6.02
Leukocyte count :		
< 4000	1	0.75
4000-11000	56	42.11
>11000	76	57.14
Thrombocyte count :		
Less than 50000/cmm	3	2.26
50001-100000/cmm	42	31.58
100001-150000/cmm	25	18.80
>150000/cmm	63	47.36
Serum bilirubin :		
1-3mg%	59	44.36
>3mg%	6	4.50
Liver enzymes :		
SGPT> 80 IU/L	56	42.11
SGOT> 80 IU/L	53	39.85
Serum Creatinine :		
> 1.5 mg%	20	15.04

Elevated INR (> 2) was found in 14(10.53%) cases.

Majority of patients (72.2%) had CSF cell counts >5 cells/cmm. Among them 56.4% patients had counts in the range of (5 – 100) /cmm, while 15.8% had counts more than 100/cmm. The highest count observed was 560cells/cmm. 27.8 % patients had CSF cell counts in the normal range (Table 4).

The biochemical parameters of Cerebrospinal Fluid (CSF) showed that majority of the cases (42.86%) had glucose levels in the normal range (50-80 mg%), 32.33% had CSF glucose level less than 50mg% and 24.81% had more than 80mg%.Micro Protein level is generally raised in scrub typhus encephalitis and in our study, 72.18% of the cases had more than 60mg%. 23.31% of the cases were in the range of 15-60mg%. 4.51% of the cases had levels below 15mg% (Table 4).

25 out of the 133 scrub typhus AES cases had pathological brain imaging (MRI) findings. Diffuse cerebral edema was the most common finding and was noticed among 11 ie, 44% cases. Less common

Table 4 — *CSF study among Scrub typhus AES cases*

CSF cell count	No of cases (n=133)	Percentage (%)
< 5 cells per cmm	37	27.8
5-100 cells per cmm	75	56.4
>100 cells per cmm	21	15.8
CSF Glucose levels	**No. of cases**	**Percentage (%)**
<50 mg/dl	**43**	**32.33**
50-80mg/dl	**57**	**42.86**
>80mg/dl	**33**	**24.81**
CSF Micro Protein	No. of cases	Percentage (%)
<15mg/dl	6	4.51
15 - 60 mg/dl	31	23.31
> 60mg/dl	96	72.18

pathological findings were progressive multifocal leucoencephalopathy, bilateral increased signal intensities in lateral ventricles and mild cerebral atrophy (2 patients each ie, 8%) Other important findings were hyper-intense signals in both parietal regions, ventricles, fronto-parietal region and on flair sequences in thalami.

Discussion

Acute encephalitis syndrome is characterized by rapid onset of febrile illness associated with convulsion, altered sensorium and focal neurological deficits such as aphasia, hemiparesis, involuntary movements, ataxia or cranial nerve palsies[8].

It is a major seasonal public health problem in many states of India including Bihar (mainly in Muzaffarpur and its adjacent districts)[9]. AES is generally caused by different neurotropic viruses. But at present CNS involvement is being reported among a substantial number of scrub typhus patients from Dehradun (Uttarakhand), Vellore (Tamil Nadu), Puducherry and Lucknow (Uttar Pradesh)[10,11].

In our present study many AES cases which were positive for scrub typhus IgM were detected from various districts of West Bengal during the period April 2018 to March 2019. In our study, 30.93% AES cases had seropositivity for scrub typhus IgM ELISA, which almost matched with the study conducted at Chennai, Tamil Nadu by Kar *et al* in 2014[12] where seropositivity was 30%. Both the sexes were almost equally affected (Male-65, Female-68) and majority of cases were reported from the rural adjoining districts of Kolkata, namely South and North 24 Parganas, Howrah, Nadia and Murshidabad.

Scrub typhus is quite common among children and

most of them belong to under-fifteen age group. In our study 90 out of 133 ie, 67.67% of the seropositive cases were below 15 years of age.

Most of the cases were reported during the months of July to December. Such a seasonal upsurge of cases has been reported earlier in other studies also[13]. This is because of two factors. Firstly the higher incidence of scrub typhus in autumn and winter may be due to increased human activities in the agricultural fields and bushes during these periods. Secondly, in the immediate post-monsoon period (September to early January), there is growth of secondary scrub vegetation, which is the habitat for trombiculid mites (mite islands)[14].

Fever is the hallmark of scrub typhus infection with various non-specific signs and symptoms. In our present study 100% patients presented with fever and it lasted for more than 7 days in most (69.17%) cases. Whereas longest duration of fever in this study was found to be two months, one patient presented with H/O only one day febrile illness before the onset of AES. Kar et al reported the onset of AES which was preceded by fever of 3 days only[12].

The other clinical features were headache (82.7%), bodyache/myalgia (78.19%), convulsions (77.44%), altered sensorium (74.44%), nausea and vomiting (50.38%), lymphadenopathy (48.12%), skin rash (36.09%), cough with/without respiratory distress (32.33%), eschar (27.07%), meningeal signs (25.56%), abdominal pain (17.29%), hemiparesis (1.50%) and pedal edema (0.75%).

In our study, 74.44% patients presented with altered sensorium and 50.38% had history of nausea and vomiting. Meningeal signs like nuchal (neck) rigidity with or without Kernig's sign was present in 34(25.56%) cases which was much less than the findings of Jamil *et al* (76.92%)[15].

Eschar, the pathognomonic feature of scrub typhus, was detected in 27.07% of patients that closely correlates with the study conducted in North East India by M D Jamil *et al* at Neigrihms, Shillong where the detection rate was 30.76%[15]. On the other hand, UK Mishra *et al*[16] found eschar among 46% scrub typhus cases. Lymphadenopathy, another important sign of scrub typhus, was noted in 64(48.12%) patients that matched with the study of Jamil *et al* ie, 46.15%[15].

Respiratory symptoms were common non-neurological findings in complicated scrub typhus infection. In our study 43 (32.33%) patients presented with cough with/without respiratory distress which is almost thrice the findings of Stalin Viswanathan *et al*[17].

Though both leucocytosis (>11000 cells/mm^3) and leucopenia (<4000 cells/mm^3) could be seen in scrub typhus, leucocytosis (57.14%) was the predominant finding in our study. Similar finding was noticed in the study of Chakraborti *et al*[13] where 48.31% had elevated leucocyte count. Normal leucocyte count was noted in 56 (42.11%) patients while only one patient presented with leucopenia (0.75%). The thrombocyte count < 150000/cmm was found in 52.64% of cases which nearly matched with the study conducted by Dr Murali Krishnan *et al*[18]. Only 3(2.26%) patients had thrombocyte count less than 50000/cmm.

Azotemia in the form of raised serum creatinine level (>1.5mg%) was found in 20 (15.04%) cases. Kidney involvement in the background of scrub typhus AES had been reported in earlier studies.

42.11% and 39.85% patients were reported to have high serum Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT) level respectively. The highest elevation for SGPT was 1250 IU/ml and that of SGOT was 840 IU/ml.

Majority (72.2%) of scrub typhus AES patients had CSF cell count >5 cells/cmm. Among them 56.4% patients had count in the range of (5-100) /cmm, while 21 patients (15.8%) had count more than 100/cmm. Mittal *et al*[19] conducted a study at Gorakhpur, Uttar Pradesh which detected 95.3% patients had cell count ranged from (5 - 100)/cmm and only 2 patients had CSF cell count >100/cmm. The aforesaid study differed from our study in terms of the nature of the study as well as the age groups of the patients included. While the study conducted by Mittal *et al*[19] was a case control study exclusively devoted to paediatric patients, ours was an observational cross-sectional study involving different age groups.

The biochemical parameters of CSF showed that majority of the cases (42.86%) had glucose levels in the normal range, ie, 50-80 mg/dl, while 32.33% of the cases had CSF glucose level less than 50 mg/dl and 24.81% cases had more than 80mg/dl. High CSF glucose level might be due to intravenous fluid administration.

Microprotein levels are found to be raised in scrub typhus encephalitis. In our study, 72.18% cases had more than 60mg/dl and the highest level noted was 680 mg/dl. 23.31% had CSF microprotein level in the range of 15-60mg/dl while 4.51% had level <15mg/dl[20].

25 out of 133 scrub seropositive cases were advised for MRI Brain and 11 of them had diffuse cerebral edema, a common finding in scrub encephalopathy[20].

Two cases each showed progressive multifocal

leucoencelopathy, bilateral increased signal intensities in lateral ventricles and mild cerebral atrophy. Hyperintensity signals were also found in both parietal regions, in both ventricles, in fronto-parietal region and on flair sequences in thalami. Hypodense lesions were seen in the PCA territory and in left parietal region which were consistent with the findings of previous studies.

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Original Article

CT Perfusion Study in Pulmonary Masses

Shyam Mohan[1], Sayan Sarkar[2], Mathews Baby Madathil[3], George Mothi Justin[4]

Purpose : To compare the Computed Tomography (CT) perfusion parameters involving malignant and benign lung lesions and of various histological types of malignant lung neoplasms.

Materials and Methods : Perfusion parameters ie Blood Flow (BF), Blood Volume (BV), Mean Permeability Surface Area Product (PS), Time to peak (TTP) and Mean Transit Time (MTT) underwent analysis. Each mean value with the 95% Confidence Interval (CI) was obtained. A "p" value of <0.05 indicates statistical significance.

Results : The mean value (lower CI- Upper CI) of BF, BV,PS, TTP and MTT in benign and malignant lesions was calculated. Similarly, the mean value with CI for each parameter was obtained for adeno carcinoma, squamous cell carcinoma, small cell carcinoma(SCC), large cell carcinoma (LCC) and metastases individually.

Conclusion : Statistically significant difference was noted between benign and malignant lesions based on BF, BV and PS. Statistically significant difference was noted between all subtypes on BV with the exception of adeno carcinoma versus SCC. BF also showed statistically significant difference between all subtypes with the exception of Squamous cell carcinoma versus LCC and SCC versus metastases.

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Key words **: CT perfusion, Blood Volume, Blood Flow, Mean Transit Time, Lung cancer.**

Lung cancer is the most common cause of cancer related death in the world, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of total number). It is the most common cancer among men with highest estimated age standardized incidence in central, Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000)[1]. Pathologically lung cancer is broadly divided into small-cell lung cancer (SCC, comprising 20% of lung cancers), and non-small-cell lung cancer (NSCLC, comprising 80% of lung cancers). SCC is a tumour of neural crest origin. NSCLC is thought to originate in lung epithelial cells and comprises diverse histological subtypes including adenocarcinoma, squamous, anaplastic and large-cell carcinomas[2].

Lung cancer presents as an incidentally detected pulmonary nodule /mass in 30-40% of cases. Distinguishing malignant and benign nodules using conventional radiography and computed tomography is a major diagnostic challenge and a large percentage of lesions show overlapping features. Since benign and malignant neoplasms differ in patterns of angiogenesis, a functional imaging modality which can reflect perfusion patterns of pulmonary nodules can be very helpful in differentiating them.

Editor's Comment :

- CT perfusion study can be taken as an important adjunct tool for characterization of pulmonary masses.
- It was observed in our study that BF, BV and PS showed statistically significant difference between benign and malignant lesions.
- BF and BV showed statistically significant difference between the most number of subtypes of malignant lesions.

Perfusion is the supply of blood to a unit volume of tissue per unit of time and usually at the capillary level. Tissue enhancement over time represents the rate and amount of contrast material distribution in the vascular space and extravascular, extracellular space. By using various mathematical models adjusted to the arterial attenuation, measurement of tissue attenuation over time can describe physiologic parameters like blood volume, blood flow rate, tissue permeability, and mean transit time. Perfusion values have shown significant differences when comparing normal tissue versus tumours and malignant versus benign lesions within the lung, liver, pancreas and bowel. In general, higher perfusion parameters were reported in patients with brain, hepatic, rectal, lung, gastric, head and neck and neuroendocrine tumours, although the angiogenic phenotype is diverse between different type of tumours and also in the same type of tumour[3].

Primary objective of the study is Comparison of

Department of Radiology, Medical Trust Hospital, Kochi, Kerala 682016

[1]DNB, Resident and Corresponding Author

[2]DNB, Resident

[3]MD, Consultant Radiologist

[4]MD, DNB, Consultant Pulmonologist, Department of Pulmonology, Medical Trust Hospital, Kochi, Kerala 682016

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Computed Tomography (CT) perfusion parameters of malignant versus benign lung lesions. Secondary objective of the study is comparison of CT perfusion parameters characterising various histological types of malignant neoplasms of the lung. Perfusion parameters used for comparison are : (1) Blood flow (BF) which means the volume flow rate of blood through the vasculature (expressed as mL/min/100 mL) (2) Blood volume (BV) ie, the volume of blood within the vasculature that is really flowing (expressed in units of mL/100mL) (3) Mean transit time (MTT) ie, average time it takes for blood to transport between the arterial inflow and venous outflow, measured in seconds (4) Permeability surface area product (PS) ie, the product of permeability and total surface area of capillary endothelium in a unit mass of tissue or tumour (measured as mL/min/100 mL) (5) Time to Peak (TTP) ie, the time at which contrast concentration reaches its maximum, in seconds.

Materials and Methods

The prospective observational study was conducted at the Department of Radiodiagnosis of Medical Trust Hospital from August, 2016 till September, 2017 after taking consent from patients and approval by the Ethics Committee. It was done to observe the characteristics of lung lesions on CT perfusion study and how the perfusion parameters differ among benign and malignant lung pathologies and also among the various histological subtypes of the malignant masses. The source of data was patients who were referred to our Department of Radiodiagnosis, for contrast Enhanced CT (CECT) thorax for evaluating pulmonary lesions. Based on the previous study[4] it was observed that the proportion of patients who have large cell carcinoma was 7.1%, precision was 8% and with 95% Confidence Interval, the minimum required sample size was found to be 40. We used here the software nMaster 2.0 and the following formula has been used for sample size calculation.

Formula

$N= z^2(1-\alpha/2)\ p(1-p)/r^2$

Where,

p : Expected proportion = 0.071

r : Absolute precision = 8

1- $\alpha/2$: Desired Confidence level=95%

N=40

Calculation

Sample size $n= [1.96^2 *0.071(1-0.071)]/\{.8\}^2=40$.

Inclusion Criteria :

Patients diagnosed with pulmonary lesions in chest Xray, who were referred for contrast CT thorax, were included in this study. Following inclusion criteria were used.

- All lesions were larger than 10mm which had no areas of fat, calcification or necrosis.
- Who did not undergo any chemotherapy or radiotherapy.
- Age more than 40 years, in view of increased radiation dose.

Exclusion Criteria

- Subjects of reproductive potential, who are sexually active but unwilling and/or unable to use medically appropriate contraception, or women who are pregnant or breastfeeding.
- Documented allergy to iodinated contrast media.
- The patient should not have any renal compromise with creatinine being less than 1.5 mg/dl and/or estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2.

Data Acquisition :

After obtaining informed consent from patients who satisfied the inclusion and exclusion.

criteria CT perfusion was performed using a 128-detector row dual energy CT scanner [General Electric (GE) Revolution, France]. A 19-gauge cannula was inserted into antecubital vein prior to the examination.

A bolus of 50 ml of iodinated low-osmolar non-ionic contrast material (Ultravist 300, Schering, Berlin Germany) was injected intravenously at the rate of 4-5 ml/sec using a pump injector (The Salient™ CT Injector, Bayer, NSW, Australia). After acquiring non-contrast High Resolution CT (HRCT) thorax, dynamic acquisitions encompassing the entire nodule (20 shuttle passes) were done around 5 s following the start of bolus injection using the following parameters:

120 kV; 80mAs; rotation time, 0.50 s; table speed 110 mm/s; detector coverage, 40.0 mm; helical thickness,5mm; field of view, 350 mm; matrix, 512X 512. Total duration time was different for various patients but was approximately 34s (30-40s). Accumulated average exam dose length product was 1639.98 mGy-cm.

Following completion of CT examination, data was transferred to a stand-alone workstation (GE Advantage 4.6) and analyzed with a commercial CT perfusion software (CT perfusion 4D).

The artery input was calculated after placing a circular region of interest (ROI) over the aorta or the left subclavian artery in case the aorta was not included in the section. Perfusion parameters of the nodule were calculated on a circular or oval ROI around the

peripheral region of lesion avoiding lung tissue with atelectasis and cavitation. The analytical method that was used in this study was based on the deconvolution model. Five major kinetic parameters were obtained (1) BV measured as ml/100ml (2) BF measured as ml/min/100ml (3) MTT measured as sec (4) PS measured as ml/min/100ml (5) TTP measured in sec. Colour parametric and composite maps of these perfusion parameters were spontaneously generated and recorded .

All lesions were biopsied under CT guidance by a senior radiologist with over 10 years of experience and histological diagnosis was made. Lesions were categorised into two groups namely malignant and benign.

Further, the malignant variety was subdivided into adeno carcinoma , squamous cell carcinoma, small cell SCC, large cell carcinoma (LCC) and metastases based on histology.

Perfusion parameters of each group were analyzed using a statistical software named International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) ver.20 to find out significant difference among various groups. Normality was checked by Kolmogrov-Smirnove test.

For independent samples Kruskal-Wallis H test was used for testing the significance among the non-parametric data. The mean and 95% confidence interval (CI) was calculated for all parameters .Pearson Chi-square test, fisher's exact test was utilised to find the relation between categorical variables. A p-value of <0.05 was taken to be statistically significant.

Results

40 patients (29 men and 11 women) with a mean age of 63 years, who satisfied the inclusion and exclusion criteria were included and taken up for CT Perfusion study. Table 1 demonstrates the sex distribution of the population. Some of the representative cases have been reported in detail, in the following section, along with their respective images.

Case Examples :

Fig 1 (1a,1b and 1c) shows the CT perfusion images of a 40-year-old male who had a lesion measuring 3 x 3cm on chest Xray. Post processing analysis of images using CT perfusion software showed following values, BF-194ml/min/100ml, BV-10ml/100ml, MTT-3.6sec and PS-27 ml/min/100ml. High perfusion parameters suggested the possibility of malignancy. A CT guided biopsy was taken from the lesion. This was proved to be adenocarcinoma histologically.

Fig 2 (2a,2b,2c,2d) shows the CT perfusion images of a 78-year-old male who had a lesion measuring 3.2 x 3cm on chest Xray. Post processing analysis of images using CT perfusion software showed following values, BV-26 ml/100ml, BF-206ml/min/100ml, MTT-2.3 sec, PS-3.8ml/min/100ml, TTP-5.8sec. High perfusion parameters suggested the possibility of malignancy. A CT guided biopsy was taken from the lesion. This was proved to be squamous cell carcinoma

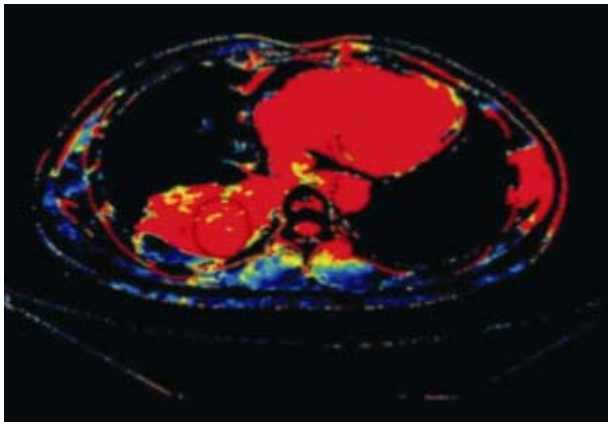

Fig 1a — Axial CT of thorax with perfusion map placed over mass in right lower lobe showing BF= 194ml/min/100ml

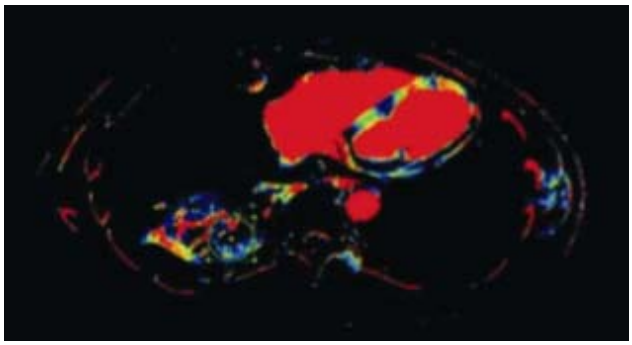

Fig 1b — Axial CT of thorax with perfusion map placed over mass in right lower lobe perfusion map showing BV=10 ml/100ml

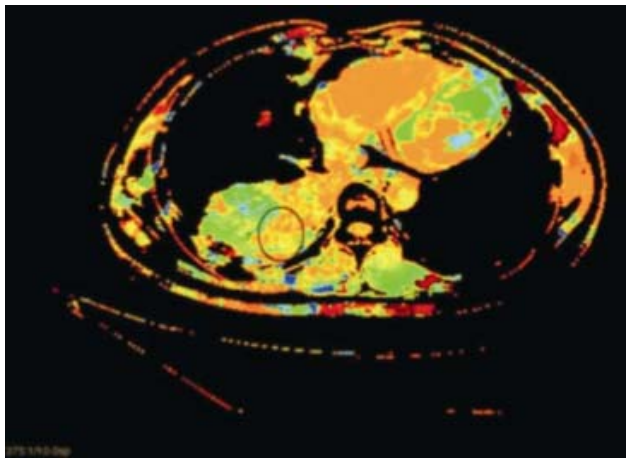

Fig 1c — Axial CT of thorax with perfusion map placed over mass in right lower lobe perfusion map showing MTT = 3.6 sec

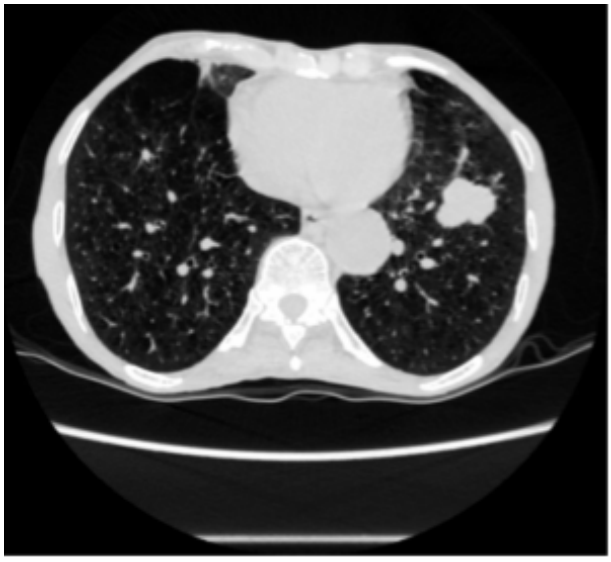

Fig 2a — Axial CT of thorax showing a mass with lobulated margins in left upper lobe

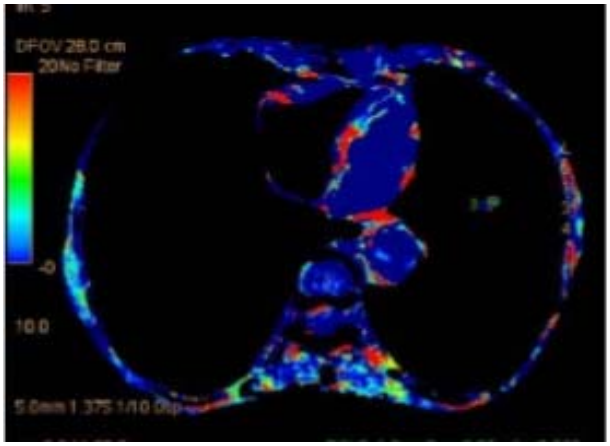

Fig 2b — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing PS=3.8ml/min/100ml

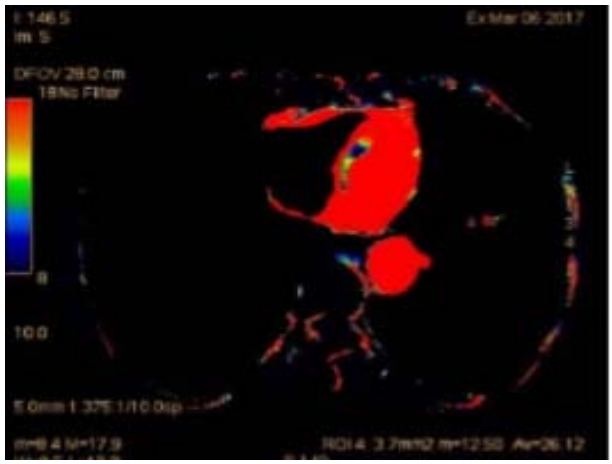

Fig 2c — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing BV= 26ml/100ml

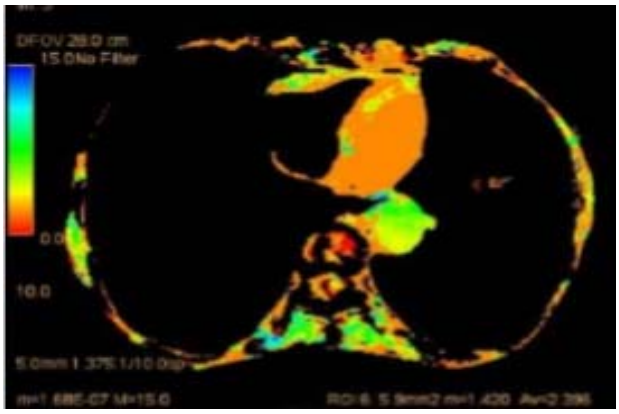

Fig 2d — Axial CT of thorax with perfusion map placed over mass in left upper lobe showing MTT=2.3 secs

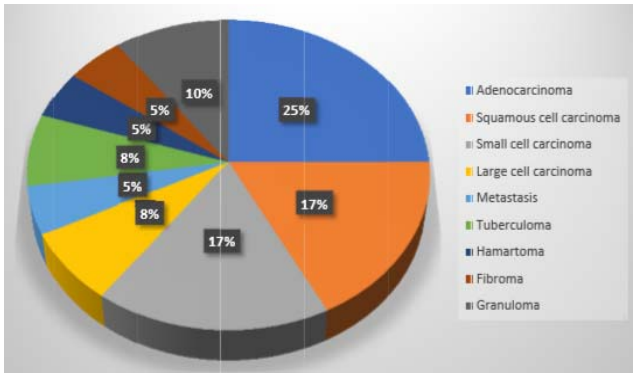

Fig. 3 — Pie chart showing histological distribution of all cases both benign and malignant

histologically.

Among 29 patients with malignancies – 10 had adenocarcinoma, 7 had squamous cell and small cell varieties each, 3 had large cell variety and 2 had metastases. The rest of the 11 patients had benign lesions which included 3 patients with tuberculoma, 2 with hamartoma, 2 with fibroma and 4 had granuloma. Fig 3 is a pie chart showing the distribution of all the lesions (benign and malignant).

Table 2 shows correlation among the various perfusion parameters. Positive correlation was found between BF with BV(r=0.566) and BF with PS (r=0.512). Negative correlation was found between BF and MTT(r=-0.225).Positive correlation was seen between BV with PS (r=0.644) and BV with BF (r=0.512).Negative correlation was seen between BV and MTT (r=- 0.836).Positive correlation was found between MTT with BV (r=0.644). Negative correlation was seen between PS and MTT (r=-0.109). Positive correlation was seen between TTP with MTT (r=0.153). Negative correlation was observed between TTP with BV (r= -0.215), TTP with BF (r=-0.299) and TTP with PS (r= -0.258).

Table 1 — *Demonstrates the sex distribution of the population*

Sex	Number	Percentage
Male	29	72
Female	11	28

Table 2 — *Correlation among the various perfusion parameters*

Correlation	Pearson Correlation Value	Type of Correlation
BF Vs BV	0.566	Positive
BF Vs PS	0.512	Positive
BV Vs PS	0.644	Positive
MTT Vs BV	0.644	Positive
BF Vs MTT	-0.225	Negative
BV Vs MTT	-0.036	Negative
PS Vs MTT	-0.109	Negative
BV vs TTP	-0.215	Negative
BF vs TTP	-0.299	Negative
MTT vs TTP	0.153	Positive
PS vs TTP	-0.258	Negative

Table 3 — *Comparison between benign and malignant lesions based on BF*

Type	Mean (ml/min/100ml) (Lower CI- Upper CI)	P value
Benign	55.0 (42.6-67.4)	0.018
Malignant	167.4 (121.5- 213.3)	

Table 4 — *Comparison between benign and malignant lesions based on BV*

Type	Mean (ml/100ml) (Lower CI- Upper CI)	P value
Benign	7.5 (4.5 -10.5)	0.024
Malignant	18.1 (15.0-21.2)	

Table 5 — *Comparison between benign and malignant lesions based on MTT*

Type	Mean (seconds) (Lower CI-Upper CI)	P value
Benign	9.9 (5.2-14.6)	0.577
Malignant	8.6 (6.5-10.7)	

Table 6 — *Comparison between benign and malignant lesions based on PS*

Type	Mean (ml/min/100ml) (lower CI-upper CI)	P value
Benign	12.0 (7.3-16.7)	0.003
Malignant	22.0 (18.9-25.1)	

Table 7 — *Comparison between benign and malignant lesions based on TTP*

Type	Mean (seconds) (Lower CI- Upper CI)	P value
Benign	16.3 (10.0-22.7)	0.064
Malignant	18.2 (14.6-21.9)	

Table 3 compares the benign and malignant lesions based on BF. Statistically significant difference was observed between malignant and benign lesions ($p<0.05$). The mean value (lower CI-upper CI) of BF was 55.0 (42.6-67.4) and 167.4 (121.5- 213.3) ml/min/100ml respectively.

Table 4 shows the comparison between benign and malignant lesions based on BV. Statistically significant difference was noted between benign and malignant lesions ($p<0.05$). The mean value(lower CI-upper CI) of BV was 7.5 (4.5 -10.5) and 18.1 (15.0-21.2) ml/100ml respectively.

Table 5 shows the comparison between benign and malignant lesions based on MTT. No statistically significant difference was observed between malignant and benign lesions($p>0.05$). The mean value of MTT (lower CI-upper CI) was 9.9 (5.2-14.6) and 8.6 (6.5-10.7) seconds respectively.

Table 6 shows the comparison between benign and malignant lesions based on PS. Statistically significant difference was noted between benign and malignant lesions ($p<0.05$). The mean value of PS (lower CI-upper CI) was 12.0 (7.3-16.7) and 22.0 (18.9-25.1) ml/min/100ml respectively.

Table 7 shows the comparison between benign and malignant lesions based on TTP. No statistically significant difference was noted between benign and malignant lesions ($p>0.05$). The mean value of TTP (lower CI-upper CI) was 16.3 (10.0-22.7) and 18.2 (14.6-21.9) seconds respectively.

Table 8 shows the mean values of the different perfusion parameters among the different subtypes of malignancy with the CI. BV and BF showed difference in value among majority of the subtypes.

Table 9 shows the p values comparing the different subtypes of malignancy based on each perfusion parameter separately. BV and BF showed statistically significant difference among the majority of different types of malignancies ($p<0.05$). Other parameters (MTT, TTP and PS) showed statistically significant difference between few subtypes.

Discussion

Only a few studies have been described in literature which used CT perfusion for characterization of pulmonary lesions and most of them did not compare the different histological subtypes of malignancy. Our study not only tries to differentiate benign versus malignant etiology based on perfusion, but also attempts to categorise the various histological varieties of malignancy. In 2008 Sitartchouk et al showed that perfusion parameters viz MTT,BF and PS showed statistically significant difference in benign and malignant nodules[5]. In our study also similar results were obtained except for MTT which did not show statistically significant difference. Roberts H *et al*[6] showed that PS value can differentiate benign from malignant nodules akin to our results. In 2007 Ruan CM *et al*[7] proved that the values of BF and BV were significantly higher in malignant masses, but MTT did not show any difference. The study by Ohno Y *et al*[4], comparing the capability of CT perfusion with combined

Table 8 — *Mean value of the perfusion parameters among the different subtypes of malignancy with the CI*

Histological Type	Mean value (Lower CI-Upper CI)
Blood Volume (ml/100ml) :	
Adenocarcinoma	13.7(8.6-18.8)
Squamous Cell carcinoma	23.0(16.1-30)
Small Cell Carcinoma	13.4(3.6-23.3)
Large Cell Carcinoma	26.8(18.4-35.1)
Metastasis	17.5((10.2-24.2)
Blood Flow (ml/min/100ml) :	
Adenocarcinoma	86.6(59.9-113.2)
Squamous Cell carcinoma	269.6(133.9-405.3)
Small Cell Carcinoma	118.9(47.5-190.2)
Large Cell Carcinoma	209.6(73.4-345.7)
Metastasis	117(80.0-144)
Mean Transit Time (seconds) :	
Adenocarcinoma	8.3(4.4-12.3)
Squamous Cell carcinoma	4.4(2.0-6.7)
Small Cell Carcinoma	8.2(3.7-12.8)
Large Cell Carcinoma	15.3(9.0-21.5)
Metastasis	16.1(10.0-22.1)
Time to Peak (seconds) :	
Adenocarcinoma	15.8(7.7-23.9)
Squamous Cell carcinoma	11.1(4.2-18.0)
Small Cell Carcinoma	23.9(18.5-29.3)
Large Cell Carcinoma	20.1(10.2-30.3)
Metastasis	17.6(5.5-29.7)
Mean Permeability Surface area product (ml/min/100ml) :	
Adenocarcinoma	20.3(14.2-26.5)
Squamous Cell carcinoma	27.1(22.7-31.5)
Small Cell Carcinoma	20.7(8.0-33.4)
Large Cell Carcinoma	20.8(11.3-30.3)
Metastasis	21.8(11.2-33.2)

positron emission tomography and CT (PET/CT) found that all results in the malignant nodule group were significantly different from that in the benign nodule group (P <0.05). Venkat *et al*[8], performed CT perfusion in eighty five patients and found strong positive correlation of BF with BV and BF with PS , and weak positive correlation between BV and MTT. They obtained higher values of BV, BF and MTT in adenocarcinoma when compared to other histological subtypes. In our study, we found significant positive correlation between BF and BV, BF and PS, MTT and BV. Further, BF and BV showed statistically significant difference between the majority of the histological varieties of malignancy. In 2016 LV *et al*[9] found that the perfusion parameters of BV, MTT, BF and PS in the lung cancer group showed significantly higher values than those in the non-cancer group.In our study also similar results were obtained except for MTT.In 2018, Hou *et al*[10],showed that levels of MTT, PS, BV

Table 9 — *P values comparing the different subtypes of malignancy based on each perfusion parameter separately*

Diagnosis	P value
BV (ml/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.07
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.04
Squamous cell carcinoma v metastases	0.03
SCC v LCC	0.04
SCC v metastases	0.03
LCC v metastases	0.04
MTT (seconds) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.06
Adenocarcinoma v LCC	0.06
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.03
Squamous cell carcinoma v LCC	0.06
Squamous cell carcinoma v metastases	0.04
SCC v LCC	0.035
SCC v metastases	0.04
LCC v metastases	0.06
BF(ml/min/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.04
Adenocarcinoma v SCC	0.035
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.04
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.055
Squamous cell carcinoma v metastases	0.04
SCC v LCC	0.045
SCC v metastases	0.07
LCC v metastases	0.045
Time to peak(seconds) :	
Adenocarcinoma v Squamous cell carcinoma	0.055
Adenocarcinoma v SCC	0.04
Adenocarcinoma v LCC	0.04
Adenocarcinoma v metastases	0.07
Squamous cell carcinoma v SCC	0.04
Squamous cell carcinoma v LCC	0.045
Squamous cell carcinoma v metastases	0.055
SCC v LCC	0.06
SCC v metastases	0.045
LCC v metastases	0.055
PS(ml/min/100ml) :	
Adenocarcinoma v Squamous cell carcinoma	0.055
Adenocarcinoma v SCC	0.06
Adenocarcinoma v LCC	0.06
Adenocarcinoma v metastases	0.06
Squamous cell carcinoma v SCC	0.045
Squamous cell carcinoma v LCC	0.04
Squamous cell carcinoma v metastases	0.045
SCC v LCC	0.07
SCC v metastases	0.08
LCC v metastases	0.07

and BF significantly increased with malignant Solitary Pulmonary Nodules (SPN)s compared to benign. Shan *et al*[11] in 2012 showed using threshold of BV,BF and PS values of more than 55 ml/100 g/min, 2.5 ml/100 g, and 10 ml/100 g/min respectively, SPNs were more likely to be malignant. In 2010, Y Li *et al*[12] proved that BF, and BV for malignant nodules was significantly higher than benign SPNs. Ma *et al*[13] showed significant difference of malignant and benign nodules using BF,BV and PS. Data from Wang *et al*[14],showed BF, BV, MTT, and PS values in benign SPN group was significantly lower than malignant.Our study showed statistically significant difference between benign and malignant lesions using BF, BV and PS.The main limitation of our study was the relatively small sample size and we did not include the pre treatment and post treatment change in perfusion parameters in our study design.

However, based on our results, we recommend use of CT perfusion to reliably differentiate benign and malignant lung lesions based on particular parameters. Further BV, BF can also differentiate between different histological subtypes of malignant lung cancer to a great extent. In appropriate cases this utility can be used as an additional tool to routine imaging evaluation for rapid diagnosis of lung cancer.

Funding : None

Conflict of Interest : None

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Original Article

Relevance of Clinical *versus* Ultrasonographic Estimation of Fetal Weight at Term — A Prospective Longitudinal Study

Barunoday Chakraborty[1], Souvik Kumar Mondal[2]

A facility based prospective longitudinal study was undertaken at B.S. Medical College, Bankura, West Bengal where three hundred admitted mothers selected from a homogenous population of the district having almost similar height and weight and all of them harbouring a singleton pregnancy at term without a risk factor or fetal anomaly had undergone diligent antenatal examination and clinical estimation of fetal weight by tape measurements of fundal heights and abdominal girths and subsequently Estimated Fetal Weights (EFW) were documented by a sonologist by ultrasound measurements with a software. After delivery the newborns were weighed by a Nursing Staff to document Actual Birth Weight (ABW). Overall the mean fetal weight at term antenatally assessed by clinical measurements was 2360 ± 313g; by ultrasonography was 2415.17±314g and the Mean Actual Birth Weight was 2712±172g. The Pearson's Correlation coefficient (r) calculated taking the three sets of values in pairs were 0.816 for clinically assessed EFW Vs ABW; 0.812 for USG assessed EFW *versus* ABW and 0.933 for clinical Vs USG assessed EFW and in all the three comparisons the p values with chi-square 't' test were <0.001 indicating a strong positive statistical correlation among the pairs. When the three sets of values were placed over scatter diagrams with the fit-line drawn over the scattered dots it was found that clinical and USG assessed EFW are in closer positive correlation to ABW when the expected birth weights were in the range of 2000-3000g as compared to below 2000g and above 3000g and both clinically assessed EFW and ultrasound assessed EFW are equally good predictors of ABW among all the groups ranging 1500 to 4000g.

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Key words **: Estimated Fetal Weight (EFW), Actual Birth Weight (ABW).**

Estimation of fetal weight has been incorporated into standard Antenatal evaluation. Its importance is emphasized in the management of high risk pregnancies like diabetic mother, vaginal birth after previous caesarean section, intrapartum management of fetuses presenting with breech presentation, suspected fetal growth restriction. EFW helps to decide optimal route of delivery, and level of hospital like Primary, Secondary or a Tertiary maternity care centre where delivery has to occur. A large proportion of perinatal mortality is related to birth weight which remains the single most important parameter that determines neonatal survival[2].

In day to day obstetric practice usually two methods are applied for prediction of Birth weight. Clinical methods based on tactile assessment of fetal size eg. Leopold's maneuvers followed by application of different equations to predict birth weight. The other is ultrasound measurement of fetal parts followed by use of software algorithms using various combinations of fetal parameters like fetal Abdominal Circumference (AC), Femur Length (FL), Biparietal Diameter (BPD), and Head Circumference (HC).

Editor's Comment :

- Antenatal assessment of Fetal Weight calculated from Fundal Height and Abdominal Girth is a valid and reproducible method comparable to sonographic estimates provided the pregnancy is singleton and non-risk.
- Clinical estimates of Fetal Weight during antenatal checkup by tape measurement of Symphysis Fundal Height and abdominal Girth during late third trimester best correlates with Actual Birth Weight when the later is in the range of 2000-3000 g.
- Clinical assessment of Fetal Weight is not a good predictor of actual birth weight when the fetus is small for Gestation age or growth restricted or Macrosomic.

Tactile assessment or palpation of maternal abdomen and thereby third trimester measurement of Fundal height and Abdominal girth despite its regular practice has been criticized by many as subjective and associated with significant predictive error in EFW[2]. However Sherman *et al* while comparing Clinical and Ultrasonic estimation of Fetal weight at Tel Aviv University in Israel had pointed out that before the introduction of ultrasound fetal weight was assessed clinically by external palpation of fetal parts and uterine contour and earlier studies[7,8] showed that 80-85% of

Department of Obstetrics & Gynaecology, Bankura Sammilani Medical College and Hospitals, Bankura 722102

[1]MBBS, DGO, MD, DNB, FICOG, Professor

[2]MBBS, MS (Obst & Gynaec), Postgraduate student, Presently Specialist Practitioner and Consultant at OM Infertility & Gynae Clinic, Kolkata and Corresponding Authors

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clinical estimates were within 500 g of the Actual Birth Weight (ABW) and 69% of estimates fell within 10% of ABW. They further said that the accuracy of predicting Birth-weight by a variety of different formulae incorporating different ultrasonic measurements has been studied extensively but no particular formula or biometric measurement had shown a superior accuracy. In general the mean absolute error of sonographically predicted Birth Weight varies between 6 and 12% of Actual Birth Weight and 40-70% of estimates fall within 10% of ABW[5,6].

Levdev[1] had developed a useful table based on linear measurements of the pregnant uterus to estimate fetal weight. He used different correlation factors for different maternal weights as well as periods of gestation and was able to achieve satisfactory results when compared to Actual Birth Weight after delivery. Following his footsteps Dare *et al* in Nigeria in 1988 followed up 498 women at term with measurement of Fundal Height and abdominal girth and found a good correlation between the EFW (3339 ±361g) and the actual birth weight (3230 ±387g) with a co-efficient of correlation 0.742 and total percentage of average-relative error of estimate was only 5.8%[1]. Johnson's formula is another method for estimation of fetal weight in vertex presentation where fetal weight (g)=height of the fundus (n Cm) X 155 n=12 if vertex is above the Ischial spine or n=11 if vertex is below the ischial spine. If the woman weighs more than 91 kg 1 Cm is subtracted from Fundal Height[2].

Today sonographic predictions are based on algorithms[2] using various ther oocombinations of fetal parameters such as abdominal circumference (AC), Femur Length (FL), Biparietal Diameter (BPD), Head Circumference (HC) both singly and in combination. Cambell, Hadlock, Warsof are the three common names in this context. Our institution uses Hadlock 2 (1985): $Log_{10}BW = 1.304 + 0.005251$ (AC) + 0.01938 (FL) 0.00004 (AC X FL).

The advantage of this technique is that it relies on linear and/or planar measurement of in-utero fetal dimensions that are definable objectively and should be reproducible. Early expectation was that this method would provide an objective standard for identifying fetuses of abnormal size for gestational age has been recently undermined by retrospective studies that showed sonographic estimates of fetal weight to be no better than clinical palpation for predicting fetal weight[2].

The current study revisits the utility of a diligent antenatal examination and clinical estimation of fetal weight when the same was challenged by ultrasound measurement with a software estimation of fetal weight done by a separate observer.

Materials and Methods

This is a facility based Prospective Observational Study undertaken at the Department of Obstetrics and Gynaecology, Bankura Sammilani Medical College, West Bengal which is a well known Tertiary Care Centre for maternity. Three hundred women who were admitted for delivery at term were selected for study with their consent. The women were all booked before their 28 wks of gestation and were followed at the Antenatal OPD. The period of study was one and a half year during 2017-18. All women were in between 18 to 45 years of age and permanent inhabitants of this district of Bankura, harbouring a singleton pregnancy without any congenital anomaly and gestational risk factor. For obvious reasons, women with obesity, multifetal pregnancy, Pregnancy Induced Hypertension,H/O Antepartum Hemorrhage, Polyhydramnios, Malpresentations like breech, transverse lie and preterm labour were excluded because Antenatal assessment of fundal height in these cases were likely to pose discrepancies to forecast anything about birth weight.

Clinical estimation of fetal weight was done in antenatal ward using a flexible tape measure calibrated in centimeters. The women emptied her bladder; lied supine; the fundal height was measured from the highest point of the uterine fundus to the midpoint of the upper border of the symphysis pubis. Measurement was made using the reverse-side of the tape up so as to forestall any bias. The Abdominal Circumference (AC) was measured at the level of the umbilicus using the same flexible tape with the reverse side up. The fundal height multiplied by the abdominal girth measurement were expressed in grams as the estimated fetal weight in individual cases (Dares Formula) Dare *et al* 1990.

The ultrasound estimation of fetal weight was done by a trained sonologist at the ultrasound room adjacent to the Antenatal ward on the same day using an abdominal sector 3.5 mHz transducer on the series 7 ultrasound machine. The patient lied in the supine position on the examination couch and the ultrasound transmission gel was poured on her abdomen. A curvilinear probe was used for fetal measured parameters ie, AC, BPD, FL. The AC was measured on a transverse section through a fetal abdomen at the level of the junction of the umbilical vein and left portal vein. The BPD was taken at the level that showed the thalami, the cavum septum pellucidum, the

intrahemispheric fissure and the third ventricle and at a point were the continuous midline echo was broken by the cavum septum pellucidum. The FL was measured by identifying the full length of the femur ; measurement was taken along the axis that showed both the round echogenic cartilaginous femoral head and femoral condyles. The fetal weight was estimated using Hadlock-2 using the observed values of HC, AC, BPD, and FL using computer software that is already installed within the ultrasound machine. The clinical estimation of fetal weight was performed by the authors using Dares formula: Cases were then followed up till delivery. After delivery the newborn was weighed by a nursing staff within 30 minutes using a standard analogue waymaster scale with a zero correction. The clinical and ultrasound estimates of fetal weight and Actual Birth Weight (ABW) of the babies were documented. Obviously the sonologist and Labour room nurse who took the actual birth weight did not have prior knowledge of clinically estimated fetal weight thus reducing the bias.

Analysis of Results

In this study 97.3% mothers were of 18 to 30 years of age and 97.4% had their heights in between 150 to 169 cms ; more than 70% were primigravida and 22.7% were second gravida. All of them were at term and 82.6% had a gestational age of 37 to 40 wks and rest was post dated by one or two weeks.

Table 1 shows the distribution of clinically Estimated Fetal Weight (EFW); ultrasound assessed EFW; and Actual Birth Weight (ABW) where they could be plotted in five different groups eg, 1500-2000g; 2001-2500g ; 2501-3000g ; 3001-3500g ; and 3501-4000g. Where the clinical assessment says 170 fetuses would be in between 2001-2500g, USG says it would be 156 fetuses- so not a big difference; but ABW shows it was only 71, ie, definitely a considerable difference.

Table 1 — *Distribution of Clinical, USG Estimated Fetal Weight and Actual Birth Weight*

EFW (g)	Clinically assessed EFW n=300	USG assessed EFW n=300	Actual Birth Weight n=300
1500 - 2000	35	27	10
2001 - 2500	170	156	71
2501 - 3000	88	107	173
3001 - 3500	07	10	40
3501 - 4000	0	0	06
Mean ± 3SD	2360±313	2415±314	2712±172
Median	2353	2406	2700
Range	1560-3500	1558-3490	1700-3800

In the 2501-3000 g where clinical assessment showed it would be 88 fetuses, USG said it would be 107- again not a big difference but ABW came out to be 173 fetuses indicating a visible underestimation by both clinical and ultrasound assessment. These visible differences with ABW with antenatal EFW was more conspicuous in the groups below 2000g and above 3000g. ie, : 35 *versus* 10 ; 27 *versus* 10 ; and 7 *versus* 40; 10 *versus* 40.

Overall the Mean Fetal Weight at term antenatally assessed by clinical measurements was 2360±313g and by USG was 2415.1±314g and the Mean Actual Birth weight postnatally observed was 2712±172g.

Table 2 shows the three relevant associations where the calculated Pearson's Correlation co-efficient (r) is 0.816 for clinically assessed EFW Vs ABW ; 0.812 for USG assessed EFW Vs ABW and 0.933 for clinical *versus* USG assessed EFW and in all the three comparisons paired chi square P value was < 0.001 indicating significant positive statistical correlations among the pairs.

Figs 1,2,3 are the three relevant scatter diagrams depicting correlations among the three relevant pairs. Fig 1 is for clinically assessed EFW Vs ABW; Fig 2 is for USG assessed EFW Vs ABW and Fig 3 is for clinical Vs USG assessed EFW. Noticeable facts here that firstly the Fit-lines in all these three scatters have a positive angle of slope indicating positive correlation between the parameters plotted over the X and Y axis ie, if the value over the X axis increases the value over the Y axis also increases in almost similar fashion.

Table 2 — *Correlation between EFW and ABW*

	Pearson's Correlation Co-efficient	p value
Clinically assessed EFW *versus* ABW	0.816	<0.001
USG assessed EFW *versus* ABW	0.812	<0.001
Clinical *versus* USG assessed EFW	0.933	<0.001

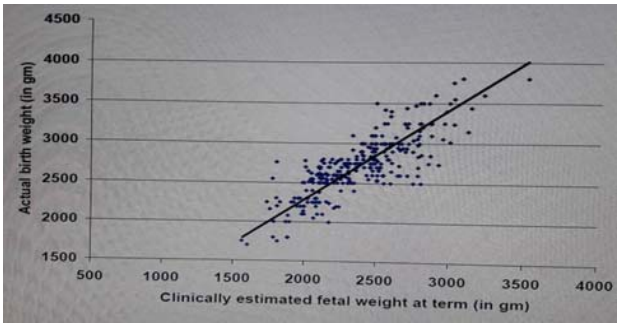

Fig 1 — Correlation of clinically estimated Fetal Weight at term and Actual Birth Weight immediately after delivery

Tab 1 correlation betwn clinlcally estmd fetal wt &abw
Tab 2 corln betwn cli efw & usg efw tab3 corrln betw usg efw & abw at term

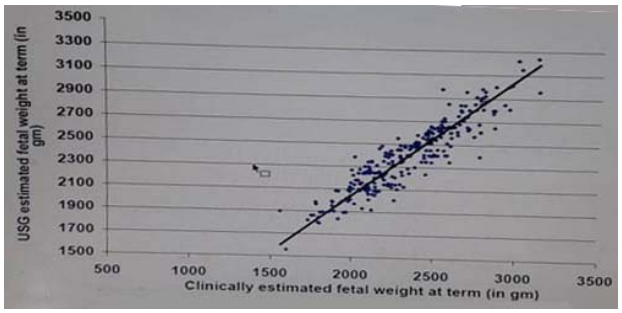

Fig 2 — Correlation between clinically estimated Fetal Weight and Ultrasound Assessed Fetal Weight at term

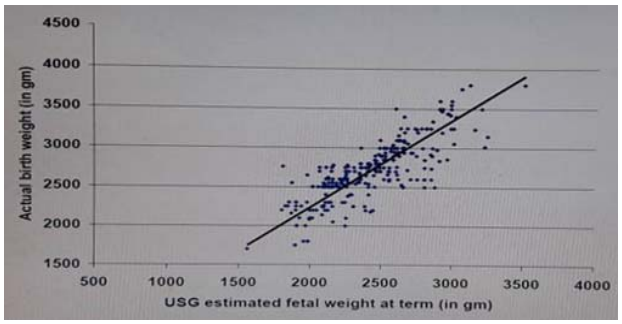

Fig 3 — Correlation between Ultrasound Assessed Fetal Weight at term and Actual Birth Weight immediately after delivery

Secondly there has been a visible crowding of dots around the fit-line in the range of 2000-3000 g in Fig 1 & 2 whereas uniform distribution of dots around the fit-line in all the weight groups can be appreciated in Fig 3 alluding to the fact that clinical and USG assessed are in closer positive correlation to Actual Birth Weight (ABW) when the expected birth weight was in the range of 2000 to 3000g as compared to below 2000g & above 3000g and both clinically assessed EFW and ultrasound assessed EFW are equally good predictors of Actual Birth Weight (ABW) among all the groups of ABW ranging 1500g to 4000g.

Discussion

Estimation of fetal weight is an important aspect of the obstetric management of high risk patients as it helps in decision making during labour to avoid complications. Estimation of fetal weight helps to identify fetuses at risk of intrauterine growth restriction which would need closer labour monitoring as well as a caesarean section in presence of a non-reassuring fetal heart rate pattern. While many obstetricians depend on ultrasound for fetal weight estimation, studies are yet to unequivocally demonstrate a significantly better accuracy for ultrasound estimated fetal weight and clinically estimated fetal weight. Moreover the paucity of ultrasonography in developing countries poses the importance of developing clinical skills for estimation of fetal weight that has been shown to be 70% accurate within 10% of ABW and compares well with ultrasound estimated fetal weight[3].

In the current study most of the participating mothers (>97%) were young (<30yrs); most of them (97%) were of average height (150-169 cms) ; more than 90% were primigravida or a second gravida and all of them were term and inhabitants of the same district – therefore they constitute a homogenous study group. Clinical and ultrasound assessment of their fetal weight correlated reasonably well when compared to Actual Birth Weight after delivery and these correlations were closer when the assessed EFW was in the range of 2000-3000g which happens to be the Actual Birth Weight in more than 80% of cases. Also clinical and ultrasound assessment were found to be statistically no different in making an antenatal forecast of fetal weight. Our correlation co-efficient (r) of 0.816 for clinical assessment and 0.812 for ultrasound assessment of fetal weight when compared to Actual Birth Weight after delivery are comparable to correlation coefficient of 0.742 for clinically assessed EFW by Dare[1] *et al* in 1988 and a correlation coefficient of 0.74 for ultrasonographically estimated Fetal Weight by Akinola *et al* at Nigeria in 2007[2].

The current study indicates that clinical estimation of birth-weight is as good as the ultrasound estimates except for low birth weight babies below 2000g.

Funding : None

Conflict of Interest : None

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Original Article

Deviations in the Basic Biochemical Parameters In COVID Patients : Our Experience in a COVID Hospital in Eastern India

Sharmistha Chatterjee[1], Ivy Ray[2], Indranil Chakraborty[3], Sujay Mistri[4]

This descriptive, observational, cross-sectional study was performed to detect the deviations in common biochemical parameters in COVID patients. All the COVID patients whether symptomatic or not (admitted within 15th of September to 30th November) were enrolled in the study. A statistically significant rise in the serum transaminases, urea, creatinine, the serum electrolytes and a decrease in serum albumin from their respective reference intervals in the population was noted. These deviations indicate that, apart from the lung parenchyma, SARS COV-2 infection affects the liver and the kidney as well. These multisystem alterations in biochemical parameters are evident even if the patients are clinically asymptomatic.

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Key words **: COVID-19, Deviations from reference intervals, Transaminitis, Multisystem alterations.**

In the month of December, 2019, a cluster of cases of atypical pneumonia now known as novel coronavirus–infected pneumonia was reported from the Wuhan city in the Hubei province in China. In the following year in early January, the causative agent of the disease was identified by the Chinese Authorities as a strain of beta coronavirus which was named as 2019 novel coronavirus (SARS-COV2) and the disease as coronavirus disease 2019 or COVID-19. The disease eventually spread out across the globe and till February 21, 2021 around 111,821,203 cases of COVID-19 and 2,475,140 deaths have been reported to the WHO[1]. The magnitude of the global spread of the disease and the havoc it wrecked on the healthcare systems across the world compelled the WHO to declare COVID 19 a pandemic on 11TH March, 2020.

Early reports suggested that it caused a severe respiratory illness similar to that caused by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[2]. Statistics associated with the disease are alarming. Almost 26 to33 per cent of patients required admission in intensive care units and there is a high mortality of 4 to 15 percent[3]. But, the majority of the patients infected with the virus are either asymptomatic or present with fever, dry cough, difficulty in breathing and chest pain of varying proportions.

Department of Biochemistry, College of Medicine and Sagore Dutta Hospital, Kolkata 700058

[1]MD (Biochemistry), FAACC, Assistant Professor and Corresponding Author

[2]MBBS, Postgraduate Trainee

[3]MD (Biochemistry), Professor and Head

[4]MD (Anatomy), Medical Superintendent *cum* Vice Principal, College of Medicine and Sagore Dutta Hospital, Kolkata 700058

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Editor's Comment :

- SARS-COV2 infection affects not only the lung parenchyma, but also other organ systems
- This multisystem involvement may be a result of hypoxia or a generalized hyperinflammatory reaction.
- Infection with SARS-COV2 causes gross biochemical derangements.
- These biochemical alterations are seen even in asymptomatic individuals infected with SARS-COV2.

In India, the first case of COVID-19 was reported on January 31, 2020 in Kerala, which increased to three cases by 3rd February; all were students returning from Wuhan. Gradually, the number of cases increased exponentially and at present, India is one of the worst affected countries inspite of a strict 21 day nationwide lockdown as a preventive measure against the pandemic which was imposed quite early in March. Till date, a total of 11,004,795 people have been affected in India and more than 149,218 people have lost their lives to the disease[4].

As mentioned previously, the clinical presentation and profile of the patients vary widely. In a country like India with a vast population and an over burdened health care system, it is imperative that the suggestive clinical picture of the COVID patient be recognised early on to prevent further mortality. In this study, we have tried to assess the deviations in the common biochemical parameters in COVID positive patients so that it may help the clinician to predict the prognosis when dealing with suspected patients.

The aim of the study was to find out the deviations in the biochemical parameters from the established reference intervals in the COVID positive patients in a dedicated COVID Hospital in Eastern India. These reference intervals were originally developed in our

departmental laboratory to cater to the population served by this Tertiary Care Hospital. Prompt diagnosis of the alterations in laboratory parameters in association with the presenting signs and symptoms will assist will careful triage of the COVID patients during the pandemic.

Materials and Methods

The following study was carried out at the College of Medicine and Sagore Dutta Hospital, Kamarhati, in the outskirts of Kolkata. All the COVID positive patients admitted in this hospital from the 15th of September to 30th November were included in the study. The COVID positive patients were included in the study within 24 hours of admission. A confirmed case of COVID-19 was diagnosed by a TRUNAAT assay of the nasopharyngeal and oropharyngeal swabs. Fasting blood samples were drawn from the patients and analysed for urea, creatinine, liver enzymes, total protein, albumin, sodium and potassium.Since, on most of the occasions, glucose was estimated in the wards by a glucometer, we did not include glucose in our study.This biochemical analysis was carried out in the Biochemistry Department with an automated analyser namely XL 340. Other relevant clinical and demographic data was retrieved from the case history and the data recorded on admission.

The data thus obtained was compiled in the excel sheet and statistically analysed.

Analyses and Results

The biochemical parameters were tabulated in EXCEL sheet and the descriptive statistics were first calculated. Almost all the parameters were non-parametric in distribution as seen in the skewness and kurtosis. The statistical analyses is given below in Table 1, Fig 1.

Discussion

A cursory glance at the table throws up some interesting data. Firstly, the tranaminases have increased considerably. 95% CI for AST and ALT are 47.55-55.5 U/l and 51.3-64.4 U/l and respectively while the reference intervals for the same are <45U/l and <35U/L .There are several theories regarding the elevation of liver enzymes. The liver damage may be caused directly by viral on slaught on the hepatic cells and some studies have demonstrated the presence of the virus in the liver cells though in the absence of viral inclusion bodies.Also gastrointestinal disturbances like diarrhoea have been reported quite frequently in these patients and the virus has been isolated in stool and blood samples[2,3]. It may also be noted here, that the Alkaline Phosphatase (ALP) has not increased correspondingly. Another plausible theory is that the hypoxia associated with the pneumonia in these patients contribute significantly to the liver injury. The ensuing cytokine storm and immune mediated inflammation in these patients may directly damage the liver. Again this hepatotoxicity has also been

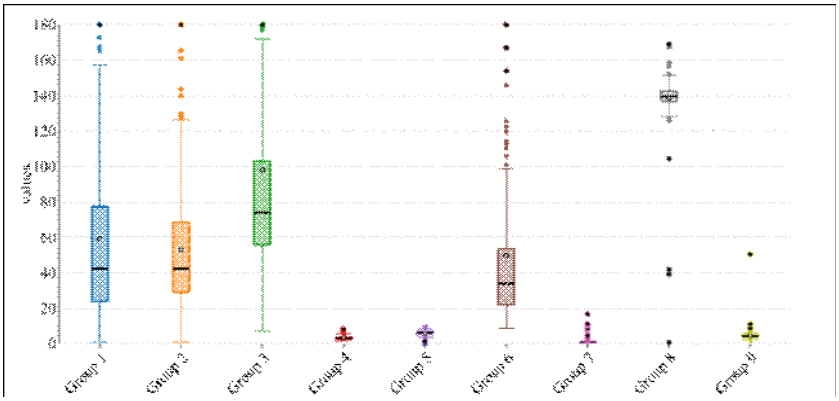

Fig 1 — Box and Whisker Plot showing the descriptive statistics of the above parameters(Groups are mentioned above in the table against the respective parameters)

Table 1 — *Showing the descriptive statistics of the biochemical parameters in COVID patients and the figure below shows the box-whisker plot.(The corresponding groups are mentioned in this table itself)*

Parameters	Mean	Median	Mode	Reference intervals	SD	95% CI
Alanine transaminase(Group 1)	57.87	41.8	16.3	M:<35 U/L F:<31 U/L	57.63	51.3—64.4
Aspartate transaminase(Group 2)	51.57	41.7	29.8	M:<45 U/L F:<34U/L	35.25	47.55—55.5
Alkaline phosphatase (Group 3)	91.99	73	52	M:53-128 F:42-98U/L	68.23	84.21—99.76
Total protein(Group 4)	5.9	6.2	6.48	6.4-8.3g/dl	1.33	5.7—6.098
Albumin (Group 5)	3.65	3.14	3.23	3.5-5.2g/dl	1.50	3.4—3.8
Urea (Group 6)	49.46	34	21.1	19-45mg/dl	58.42	42.8—56.12
Creatinine (Group 7)	1.42	0.835	0.81	F: 0.9-1.1mg/dl M:0.6-1.2mg/dl	2.98	1.75—1.80
Sodium (Group 8)	139.1	139.7	137.4	136-145meq/L	10.15	137.95—140.26
Potassium (Group 9)	4.56	4.39	4.2	3.5-5.1meq/l	2.31	4.29—4.82

[Abbreviations: M-males, F-females; SD- standard deviation; 95%CI- 95 percent confidence intervals]

attributed to drugs by some authors though raised transaminases have been documented in drug naïve patients as well. But, this liver damage is transient and usually tends to reverse on its own. Nevertheless, this reversible rise in tranaminases in COVID patients is almost universal and has been referred to as transaminitis by some authors[5-7].

Secondly, the serum urea and creatinine alongwith sodium and potassium have also increased considerably. In this study, the 95% confidence interval for urea was 42.8-56.12mg/dl, creatinine was 1.08-1.75mg/dl, serum sodium was 137.95-140meq/L and serum potassium was 4.3-4.8meq/l respectively.The reference levels for the parameters are 19-45mg/dl,0.6-1.2mg/dl,136-145meq/dl and 3.5meq/dl-5.1meq/l respectively. All these suggest a possible renal injury by the SARS-COV2. Incidentally, the Angiotensin-converting Enzyme 2 Precursor (ACE2) receptor which is considered to be a functional receptor of SARS-COV 2 has also been detected in the proximal tubules, afferent arterioles, collecting ducts, and the thick ascending limb of Henle but not so in the in distal tubules[8,9]. Studies have shown that SARS-COV2 can directly induce acute kidney injury by infecting the renal tubular epithelium and podocytes and causes acute tubular necrosis[10,11]. In COVID-19 subjects with renal function impairment, the NP antigen has been detected in the cytoplasm of kidney tubules instead of glomeruli .This acute kidney injury is actually a part of the multiple organ dysfunction syndrome caused by the activation of the immune system resulting in the release of large amount of proinflammatory cytokines TNF-α, IL-1, IL-6, interleukin (IL)-12, and interferon (IFN)-α as a part of the cytokine storm. Pathologically, inflammation and edema of the renal parenchyma has been demonstrated in patients with COVID-19[12]. Clinically the patients present with hypoperfusion, more fluid accumulation and lesser urine output[13]. The use of nephrotoxic drugs may also contribute to the scenario but the effect has not been studied in detail.

The deviations observed in these parameters indicate that the SARS COV 2 infection not only affects the lung parenchyma, it also wrecks havoc on the liver and the kidney as well. It remains to be seen however, whether this multisystem involvement is due to the hypoxia generated by the affected lung, or is a result of a generalised multisystem hyperinflammation .Whatever may be the cause, autopsy findings have demonstrated widespread micro-thromboses in large and small vessels,acute tubular injury in the kidneys,reactive lymph node changes, atypical changes in the liver histology, all supporting multisystem manifestations[14,15].

Conclusion

Thus it may be safely concluded that persons infected with SARS-COV2, show gross derangements in the biochemical parameters irrespective of the fact whether they exhibit signs and symptoms of the disease or not. In addition, it may also be concluded that there is a generalized multisystem involvement in COVID patients as evidenced by the alterations in the parameters included in the liver function tests and also the rise in urea, creatinine,sodium and potassium.

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Review Article

Diabetes and Stress

K K Pareek[1], Girish Mathur[2], G D Ramchandani[3], Rahul Ramchandani[4], Divyansh Mathur[5]

Diabetes Mellitus (DM) is a complex metabolic disease which also affects psychological condition of body. Stress is such common psychological condition which is usually related to lifestyle but it can be associated with Diabetes in many ways. DM increases stress in your body and stressful condition also leads to DM. In DM, glycemic control is certainly a primary therapy approach in management but along with that psychological conditions especially stress, depression, anxiety should be addressed equally for long term continuation of therapy. DM and stress both conditions can affect each other so medical and social comprehensive approach with involvement of patient, physician, family person, counsellors, dietician, educators, psychologists; will certainly help to manage both DM and stress and to maintain patient wellbeing also.

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Key words **: Diabetes Mellitus, Stress, Psychological condition, Depression, LSM**

Diabetes Mellitus (DM) is a metabolic condition which resulted due to elevation of blood sugar in body, which affects multiple systems of the body, which also includes psychological condition of body. According to current lifestyle pattern due to lack of exercise, higher intake of junk food, sedentary lifestyle; new onset of diabetes is continuously increasing in entire world. Stress is commonly related to lifestyle like difficulty in family, disturbed relationships, extensive work in job etc. Diabetes and stress are conjoined conditions. DM increases stress in your body and if you are stressful then it leads to DM[1]. Management of stress is very important approach in treatment of DM. Ill-treated stress leads to depression, which increases suicide tendency. If stress is not properly taken care then it causes hormonal dysregulation and worsens control of DM, which leads to various complications like cardiovascular disease (CVD), diabetic kidney disease, neuropathy etc[2].

[1]MD, FRCP(London), FACP (USA), FRCP(Glasg), FRCP(Edin), FRSSDI, FICP, FFIACM, FGSI, FDI, Senior Consultant Internal Medicine, S N Pareek Memorial Hospital & Research Center, Kota, Rajasthan 324005

[2]MD, FRCP(London), FRCP(Glasg), FRCP(Edin), FACP(USA), FRSSDI, FIACM, FDI, FICP, Senior Consultant of Internal Medicine, Alka Diagnostic Center, Kota, Rajasthan 324009 and Corresponding Author

[3]MD, FACE, FACP, FRCP(Edin), FRCP(Glasg), FRSSDI, FICP, FIACM, FDI, FGSI, Professor and Head, Department of Internal Medicine, Daswani Dental College, Kota, Rajasthan 325003

[4]MBBS, Vardhman Mahaveer Medical College and Safdarjung Hospitals, New Delhi 110023

[5]MBBS, NKP Salve Institute of Medical Sciences, Nagpur, Maharashtra 440019

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Editor's Comment :

- DM and Stress both can affect each other.
- Stress like condition should be considered in DM management.
- Proper counselling is a key approach.

Prevalence of DM and Stress:

Globally, 463 million population is living with diabetes mellitus, where in china has highest number of DM population, followed by India which has 77 million diabetic population[3]. World Health Organization (WHO) mentions that globally leading responsible risk factor for disability is may be mental disorders. Depression, Anxiety and stress, these three are leading causes of disability in young people with age <45 years[4]. According to various study, one in five adults are suffering from any mental illness, while one third of adults are suffering from stress[5]. Stress is commonly associated with conditions like female sex, advance age, obesity, DM[6]. DM and stress are commonly associated conditions, and prevalence of high/very high stress is 35% among DM patients. Major stress inducers are related to family, work, financial issues, and the disease[7].

Relationship between DM and Stress :

Relation of stress and depression with pathophysiology of type 2 diabetes mellitus is always a mystery. Multiple studies have observed that depression is associated with progressive insulin resistance and hyperglycemia, whereas the association of stress with diabetes is less clear. The biological systems involved in adaptation that mediate the link between stress and physiological functions include the hypothalamic–pituitary–adrenal axis and

the autonomic nervous and immune systems. The hypothalamic–pituitary–adrenal axis is a tightly regulated system that represents one of the body's mechanisms for responding to acute and chronic stress (Fig 1). Depression is associated with cross-sectional and longitudinal alterations in the diurnal cortisol curve, including a blunted cortisol awakening response and flattening of the diurnal cortisol curve which is also contributing factor for more resistance to insulin and high blood sugar level[8].

DM and Stress : Both Can Affect Each Other

Diabetes mellitus is a chronic metabolic condition, which leads to do major changes in lifestyle of human. Lifestyle modifications plays very crucial role in management of DM which includes diet control, proper exercise, meditation, avoidance of junk food, alcohol, tobacco. Its management also includes lifetime medications like insulin injections, oral antidiabetic agents, statin, blood pressure lowering agents[9]. Such kind of long term treatment creates social discomfort specially in young population which create social and emotional fatigue. And eventually such situation leads to "frustration of chronicity" and behavioral change like stress or depression[10]. This stress becomes itself inducer for high / very high stress. Sometimes patient may feeling himself as family burden, isolated from society, while some of patients may become aggressive or hostile to family members, clinicians or paramedical healthcare staff. In order to maintain self-esteem, the patient avoids dealing with reality, calming, in his fragility, that he is omnipotent and refusing treatment, which leads to long term complications of DM and it again potentiates condition of stress[11].

Correlation between stress and DM development is still questionable but in Fig 1, it is hypothesized that stress activates neuroendocrine related hormones and elevates their level which may cause sever hyperglycemia and require appropriate treatment of patients through anti-diabetic agents[12]. Stress develops continuous negative thoughts through vicious cycle of low adherence to therapy, nervousness, poor therapy target achievement in patient and reduces capacity to cope up with upcoming challenges in future. Early intervention and involvement of family for the treatment of DM and stress give good results in terms of adequate compliance, positive attitude of the patients' towards diabetes; which helps to control sugar level in range and reduce stress related complications as well[13-15].

DM and Stress : Therapeutic Approach

In current scenario, DM management should have holistic approach, which should not be limited to control

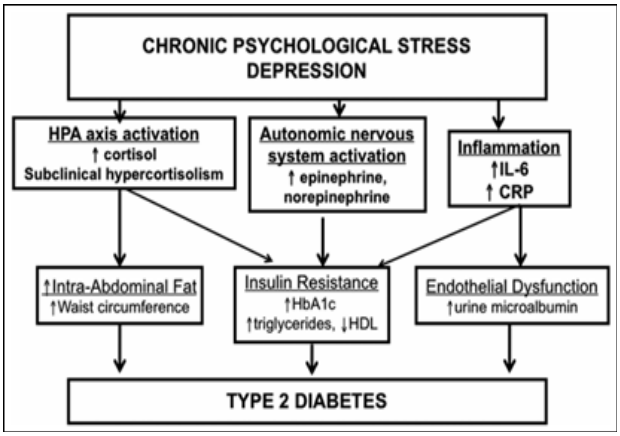

Fig 1 — DM and major mental disorders – A hypothesis

only blood sugar level but beyond that there is need to care of psychological status as well. It is requirement to establish collaborative relationship between physician and patient for appropriate long term management. The main objective of treatment to develop self-esteem in patient, and make him so capable to take proper decision for him and his family both. It is a real challenge to counsel patients regarding acceptance of this disease. It is therefore important to involve family person, dietician, psychologist, diabetes educator to make capable the patient to adjust with lifestyle changes. It was observed that important factor in adherence to strict diets as well as in blood glucose control family support was the most[16]. It is very important for patient to express his fear for future, anger, frustration and for that proper counselling is required for him[17]. As per American Diabetic Association (ADA) guidelines on clinical practice and management of DM, there are some situations where there is a need to approach mental health provider for DM patients[18].

- Impaired self-care of patient
- Positive screening for depression symptoms
- Suspicion of eating or behavioral eating disorders
- Intentional omission of insulin or oral medication to reduce weight
- Positive screening for anxiety and fear of hypoglycemia
- Suspected for serious mental illness
- Suspected for cognitive impairment
- Not able to take care for diabetes related complication
- In some cases, before undergoing bariatric or metabolic surgery and after surgery

Controlling a stress is very crucial approach in management of DM, as uncontrolled stress certainly increases blood sugar level, which may have other long

term metabolic complications in patient. Apart from medications, stress management through social cognitive theory may help to decrease stress and increase coping self-efficacy, stress management, perceived social support, and lead to a reduction in the glycosylated hemoglobin levels among patients with diabetes[19].The Mindfulness-Based Stress Reduction (MBSR) program is a approach which is utilized to treat various chronic disorders such as anxiety, depression, pain, cancer, skin diseases, immune disorders, and diabetes[20]. The concept of the "mindfulness theory" provides insight into how thoughts and emotions impact our health, emotional wellbeing, and quality of life. A patient learns how to focus on a specific target, which causes changes in some specific regions of the patient brain associated to his/her memory, sense of self, empathy, and stress[21].

Conclusion

DM is such a chronic disease which should not consider only as metabolic disorder but it has significant impact on psychosocial condition of patient as well. Glycemic control is certainly a primary therapy approach in DM management but along with that psychological conditions especially stress, depression, anxiety should be addresses equally for long term continuation of therapy. DM and stress both conditions can affect each other so medical and social comprehensive approach with involvement of patient, physican, family person, counselors, dietician, educators, psychologists; will certainly help to manage both DM and stress and to maintain patient wellbeing also.

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Review Article

Vomiting in Children : How to Identify the Surgical Masqueraders ?

Bindey Kumar[1], Manish Kumar[2], Amit Kumar Sinha[3], Mokarram Ali[4], Utpal Anand[5], Anil Kumar[6]

Vomiting in children is a common problem and some of causes include surgical conditions, which require intervention. The spectrum of cases which presents with vomiting are different from adult population. Vomiting due to surgical conditions vary from common conditions like pyloric stenosis to uncommon conditions like splenic torsion and superior mesenteric artery syndrome. Newer imaging modalities of diagnosis ranges from conventional imaging to nuclear scan and in some cases diagnostic laparoscopy.

To identify these potentially salvageable conditions require recognition of red flag signs which indicates these conditions. This review will discuss common surgical conditions presenting with vomiting in children and an algorithm is proposed to workup these cases.

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Key words **: Vomiting, Bilious, Non-bilious, Malrotation, Hirschsprung's Disease.**

Vomiting in children attracts more attention when associated with other systemic involvement like ear, nose and throat infection, urinary tract infection, meningoencephalitis and pneumonia. Hence, it is pertinent for pediatric health care providers to have a high index of suspicion for such potentially fatal surgical entities masquerading in the mundaneness of vomiting. It is imperative to intervene early in vomiting child if surgical etiology is under consideration if presents with red, bilious or feculent color, projectile nature with associated hemodynamic instability. Future management strategy of cases aims more specific procedures based on better understanding of underlying pathophysiology and may include more minimal invasive approach including robotic surgery[1].

Vomiting is one of the most common presentations in pediatric emergency department[2]. The multitude of etiologies for vomiting in children range from benign, self-limiting conditions to life threatening surgical emergencies[3].

The rationale of this narrative review is to highlights features which are harbinger of sinister outcome among those appears innocuous and normal looking vomiting in children.This article attempts to focus on vomiting in children caused by conditions warranting surgical intervention by reviewing a systematic approach to establish the 'red flag' signs and symptoms (Table 1) pointing towards a possible surgical etiology along with summarizing the pathophysiology and key features of common surgical conditions presenting as vomiting in

Editor's Comment :

- Vomiting in children is a common problem.
- Diagnostic dilemma remains when it is prolonged and recurrent.
- To identify surgically correctable conditions, high index of suspicion is required.
- In the history enquiry should be made about colour of vomiting, whether blood is there or associated localised pain in abdomen.
- During examination, visible peristalsis,localised tenderness, palpable mass, high pitched bowel sounds alongwith haemodynamic instability are suggestive of underlying surgical aetiology.

Table 1 — *Red flag Symptoms and Signs*

Symptoms :
■ Bilious Vomiting
■ Acute, Localised Pain Abdomen
■ Drawing up legs with incessant cry
■ Hematemesis
■ Haematochezia
Physical Signs :
■ Visible Peristalsis
■ Localised Tenderness
■ Palpable mass
■ High Pitched Bowel Sounds
■ Haemodynamic Instability

[1]MBBS (Hons), MS, MCh, DNB, MNAMS, PGDHM, Proessor & Head, Department of Paediatric Surgery, AIIMS, Patna 801507
[2]MBBS MD, Associate Professor, Department of Paediatric Medicine, AIIMS, Gorakhpur 273008
[3]MBBS, MS, MCh, Associate Professor, Department of Paediatric Surgery, AIIMS, Patna 801507
[4]MBBS, MS, MCh, Assistant Professor, Department of Paediatric Surgery, Pt BDS University of Health Sciences, Rohtak 124001
[5]MBBS, MS, MCh, Associate Professor, Department of GastroIntestinal Surgery, AIIMS, Patna 801507
[6]MBBS, MS, Additional Professor and Head, Department of Trauma & Emergency and General Surgery, AIIMS, Patna 801507
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children.The emphasis is focused on identifying underlying morbid aetiology in the form of obstructive, motility disorder, inflammatory and conditions which gives rise to compromised vascularity of gut.

Pathophysiology

The pathophysiology of vomiting is mediated by the lateral medullary reticular formation of the midbrain. Afferents to this vomiting center originate from at least four different sources which include chemoreceptor trigger zone (CTZ) or area prostema; vestibular system; vagal afferents and higher cortical centers such as amygdala[4]. The neurotransmitter receptors involved include muscarinic (M1), dopamine (D2), histamine (H1), serotonin (5HT3) and substance P (neurokinin 1). In case of emesis caused by surgical conditions, the afferents are primarily through the vagal fibers which are activated by abdominal distension and bowel irritation. In case of unabated emesis leading to hemodynamic compromise, CTZ may also get activated.

Systematic Approach To Vomiting

Is it Vomiting ?

The first step in evaluation of concerns of vomiting in children, especially infants, is to establish whether it's true vomiting or an age defined physiologic response such as regurgitation. Unlike vomiting, in regurgitation, the stomach contents are brought to mouth without contraction of abdominal and diaphragmatic musculature[5]. Regurgitation is a physiologic attribute, with no adverse impact on infant's growth, which mostly resolves by infancy and does not warrant intervention, medical or surgical.

What are the Characteristics of Vomitus ?

Bilious vs non-bilious : One of the strongest pointers for a possible surgical etiology for vomiting is bilious nature of vomit which indicates a possible post-ampullary obstruction until proven otherwise[6]. Bilious vomiting in newborn is seen in 6 per 10,000 live births, always raises suspicion of surgical aetiology[7]. However, Cullis *et al* reported that only 11.7 % of all cases of bilious vomiting have underlying surgical pathology[8]. It is, however, pertinent to recognize that proximal obstructions such as idiopathic hypertrophic pyloric stenosis present with non-bilious vomiting. Table 2 summarizes different causes of bilious and non-bilious vomiting.

Projectile or non-projectile : Projectile vomiting is generally indicative of sinister causes such as meningitis, conditions giving rise to raised intracranial pressure and metabolic diseases from medical perspective. For a surgeon, a persistent projectile vomiting in 3rd to 6th week of life is characteristic of infantile hypertrophic pyloric stenosis (IHPS).

What are the Accompanying Symptoms ?

Abdominal pain: Abdominal pain associated with vomiting is a common feature for both medical and surgical etiologies of emesis; however, acute, localized pain may signify the peritoneal involvement in visceral inflammation such as appendicitis.

Incessant cry : An inconsolable infant with emesis requires emergent evaluation for sinister causes such as intussusception or incarcerated inguinal hernia. Drawing up of legs with incessant cry in an infant can be subtle pointer towards intussusception.

Abdominal distension : Distension of the abdomen may be suggestive of bowel obstruction but it may arise out of gastroparesis caused by sepsis or hypokalemia.

Hematemesis : Presence of upper gastrointestinal bleed may point towards surgical emergencies such as Mallory Weiss tear.

Hematochezia : It is a common accompaniment of mucosal disease of large bowel such as inflammatory bowel diseases but if present in an infant with emesis, hematochezia requires evaluation for intussusception.

What are the Accompanying Signs ?

Visible peristalsis : Presence of visible peristalsis across abdomen or a visible 'olive' is characteristic of IHPS[9].

Table 2 — *Vomiting in Children*

Acute		Chronic	
Bilious	**Non-bilious**	**Bilious**	**Non-Bilious**
Intestinal atresia/webs	Infantile Pyloric Stenosis	Malrotation with midgut volvulus	Adrenal Crisis
Meconium Ileus	Pyloric Atresia	SMA Syndrome	Raised Intracranial Pressure
Intussusception		Meckel's Diverticulum	Appendicitis
Anorectal atresia		Hirschsprung disease	Necrotising enterocolitis
Incarcerated Hernia		Bands and adhesion	

Abdominal tenderness : Localized abdominal tenderness helps in localization of underlying visceral inflammation; while a diffusely tender abdomen with guarding or rebound tenderness points towards peritonitis.

Palpable masses : Certain characteristic findings on palpation can provide crucial diagnostic clues. A palpable 'olive' at the lateral border of rectus abdominis is consistent with hypertrophic pyloric stenosis while if a 'sausage shaped' mass is felt in right upper quadrant, intussusception should be considered.

Bowel sounds : Bowel sounds may be increased in bowel obstruction or absent in case of ileus. High pitched bowel sound are also indicative of intestinal obstruction.

Inguinal and genital signs : A tender, non-reducible inguinal mass with erythema of overlying mass is suggestive of incarceration of inguinal hernia. Swollen, tender, retracted, bluish testicle is the classical description of torsion of testis.

Specific signs : Empty or scaphoid right lower quadrant of abdomen is characteristic of intussusception (Dance sign).

Acute or Chronic Vomiting :

The duration of vomiting which is described as acute is 24-48 hours. The common spectrum of pathologies which give rise to acute presentation of vomiting are rotational anomalies of gut, congenital metabolic abnormalities,enterocolitis induced by food protein. Dehydration is common feature.

Longer duration of vomiting qualifies for chronic criteria and these presents rarely with features of dehydration and dyselectrolytemia. Common etiologies includes gastric erosion, peptic dyspepsia and hepatobiliary pathologies[10].

Clues from Imaging :

X-ray abdomen: X-ray abdomen is the quickest modality to look for mechanical bowel obstruction in child with emesis. However, the classical features of dilated bowel loops and stacked air-fluid levels may not be present in all cases. In case of intussusception, paucity of gas in right lower quadrant is strong pointer while presence of gas in cecum excludes intussusception[11]. Presence of bowel gas in hemiscrotum is suggestive of incarcerated hernia. Gas in the intestinal wall ie, pneumatosis intestinalis is seen in necrotizing enterocolitis.The pitfalls of plain imaging needs reiteration as entities like malrotation of gut or hypertrophic pyloric stenosis may have normal X-ray abdomen.

Upper GI series : Role of upper GI series is helpful in delineation of anatomy and is considered useful in conditions such as midgut volvulus with malrotation of gut or IHPS.

USG Abdomen : USG abdomen is the most utilized imaging modality in evaluation of surgical causes of emesis. It allows direct visualization of a hypertrophied pylorus and is a sensitive modality to document malrotation of gut. USG with color doppler is the diagnostic modality of choice as it localizes the site of intussusception along with estimating the vascular perfusion of involved gut.

CT abdomen : CT scan allows anatomical delineation and has definite role in evaluation of malrotation of gut, appendicitis or pancreatic pathologies.

Diagnostic Laparoscopy :

Role of diagnostic laparoscopy especially in cases of early appendicitis, malrotation of gut, Meckel's diverticulitis, early cases of intussusception has been emphasized recently. In situations of pain abdomen having diagnostic dilemma diagnostic laparoscopy helps.

Common Surgical Conditions in a Child with Vomiting

Infantile Hypertrophic Pyloric Stenosis :

IHPS typically presents around 6th week of life with non-bilious, postprandial, forceful vomiting. It has a global incidence of 2-3 per 1000 live births and is more common in male infants. For this multifactorial entity, postulated etiology include genetic factors and environmental influences such as use of macrolides. The incessant vomiting may lead to disturbances of fluid and acid-base homeostasis – hypochloremic metabolic alkalosis with paradoxical aciduria. Diagnosis is based on USG where a pyloric muscle thickness greater than 3-4mm or pyloric muscle length greater than 15-19mm is suggestive of IHPS. Definitive management is pyloromyotomy after correction of dehydration and electrolyte abnormalities[12]. Laparoscopic pyloromytomy results are comparable to open pyloromyotomy[13].

Midgut Volvulus with Malrotation of Gut :

Malrotation of the gut results from interrupted embryological process of rotation of embryonic gut. Incomplete rotation of gut and its aberrant fixation predisposes to torsion and obstruction and presents as midgut volvulus. The most common presentation is bilious vomiting. Other clinical features include abdominal tenderness and distension along with features of hemodynamic compromise. Upper GI series has been traditionally considered the diagnostic

modality of choice but USG has been shown to be equally optimal diagnostic tool[14]. Management is focused on establishing hemodynamic stability. Surgical exploration with Ladd's procedure is the definitive treatment.

Intussusception :

Intussusception is the most common cause of intestinal obstruction in children less than 3 years of age which results from invagination of a bowel segment (intussusceptum) into adjacent distal segment (intussuscipiens) and if untreated, leads to catastrophic consequences of bowel ischemia resulting in necrosis, perforation and peritonitis[15]. The classical presentation is of colicky abdominal pain, red currant jelly stool and a palpable mass. Vomiting is one of the most common symptoms of intussusception and is seen in 70% of cases. A high index of suspicion is must in children with vomiting with or without diarrohea, rectal bleeding abdominal pain accompanied with altered mental status. USG with color doppler is the diagnostic modality of choice as it not only delineates the site of intussusception but also ascertains complications such as poor vascular perfusion in affected segment. Nonsurgical reduction by instilling a contrast medium such as air, barium or saline, is the treatment of choice in a child with intussusception who is hemodynamically stable and has no evidence of perforation or peritonitis. Surgical intervention in form of open laparotomy and manual reduction of intussusception is needed only in cases where nonsurgical reduction fails or child is hemodynamically unstable with signs of perforation & peritonitis.It has been seen that after successful enema reduction in 12.7% cases recurrence may occur.

Incarcerated Hernia :

Incarceration of inguinal hernia mostly occurs in infancy and is more common in girls. Typical presentation is of an incessantly crying infant with vomiting and abdominal distension. Examination reveals a tender inguinal mass extending upto scrotum or labia majora with erythema of the overlying skin. USG is the diagnostic modality of choice. Manual reduction is attempted in all children with no signs of peritonitis. Surgical reduction is rarely needed as manual reduction is successful in >95% of cases. Once the inflammation is subsided herniotomy should be done in the same admission.

Appendicitis :

Appendicitis is the most common surgical cause for emergent surgery. Though the defining symptom of appendicitis is pain abdomen, emesis is the second most common clinical presentation of appendicitis in young children. Other classical features include periumbilical pain with migration to right lower quadrant, fever, and anorexia. Examination reveals right lower quadrant tenderness. The underlying inflammatory pathology is reflected in leukocytosis and rise of acute phase reactants. Multiple clinical scoring system such as pediatric appendicitis score, Alvarado score are used in diagnostic algorithms. Imaging modalities utilized include USG and CT abdomen. Management focusses on fluid therapy and analgesia. Appendectomy is the definitive surgical intervention. Laproscopic appendectomy is now getting acceptance with comparable intra – or postoperative complications[16].

Hirschsprung's Disease :

Hirschsprung's disease presents in early infancy with features of distal bowel obstruction,The main symptoms are constipation, abdominal distension and vomiting which may be nonbilious to start with and changing into bilious later. Etiopathogenesis includes either arrest of caudal migration of neural crest cells which give rise to ganglion cells or disruption in maturation into ganglion cells[17]. Many genetic mutations have been attributed in the development of HD mainly endothelin, glial cell line-derived neurotrophic factor, RET proto-oncogene and also SOX-10 gene[18,19]. Enterocolitis may be a life threatening complication with features of high degree of pyrexia, vomiting, diarrhea and abdominal distension. The management of HD has seen evolution through multi staged pull through surgery to single-stage transanal pull-through with comparable results.

Superior Mesenteric Artery Syndrome :

SMA-syndrome is a functional obstruction of third part of duodenum due to vascular compression by superior mesenteric artery as it takes origin from abdominal aorta an angle of less than 25 degree than normal of 45 degree. Entrapment of third part duodenum between superior mesenteric artery and abdominal aorta leads to dilatation of second and third part of duodenum[20].

It has been precipitated by excessive weight loss in short time, corrective surgeries of spine and immobilization in body casts, burn, postoperative state and accidents. Patients present with abdominal pain,post prandial bilious vomiting and early satiety. Diagnostic workshop includes upper GI contrast studies, CECT abdomen or contrast enhanced angiography or magnetic resonance angiography. Failure of conservative management through nutritional

support is an indication of surgical intervention in the form of duodenojejunostomy either open or laparoscopically[21].

Meckel's Diverticulum :

Meckel's diverticulum in children presents most commonly with features of gastrointestinal obstruction and gastro-intestinal bleeding. Inflammation in the form of diverticulitis is an uncommon presentation. Laparoscopic method is also being undertaken for managing a case of meckel's diverticulum[22].

Gastric Volvulus :

Vomiting is main presentation and diagnosed by imaging with the help of barium. Surgical intervention is done in the form of gastropexy and gastrostomy. Some cases require gastric resection. Esophageal narrowing was common post-operative complication[23].

Pancreatic Injury :

Severe pain abdomen and relief in pain in stooping position with vomiting is a common presentation. Serum amylase and serum lipase are raised. Multidetector CT scan is very accurate in diagnosis. Conservative management proves effective in hemodynamically stable cases. Pancreatic injury which is confined to proximal part can be better managed by roux-en-y pancreaticojejunostomy in distal part[24].

Raised Intracranial Pressure :

Any space occupying lesion in the cranium, head injury can give rise to nausea and vomiting by compression of medullary area postrema due to raise intracranial pressure. The presentations will be vomiting, headache, change in mental alertness and may be associated with neurological deficit. The vomiting in thse case are characterized by projectile, no accompanying nausea and precipitated by abrupt change in body posture. Fundus examination to see papilledema along with CT head or MRI brain can show herniation, enlarged ventricles or tell-tale sign of mass effect. Management include measures to reduce intracranial pressure and treatment of underlying cause[25].

Adrenal Crisis :

It is one of the important entity giving rise to vomiting in infancy presenting between first and fourth weeks of life. Usually babies have nonbilious vomiting with metabolic picture of hyponatremic, hyperkalemic acidosis associated with unexplained hypotension. Mostly it is due to 21-hydroxylase deficiency giving rise to congenial adrenal hyperplasia. Female patients may have disorder of differentiation in external genitalia. Low cortisol level in plasma alongwith high ACTH level may be seen in some cases.Electrolyte imbalance correction and hormonal supplementation is needed in these cases[26].

Author's Experience :

Our experience where, in six years, from June, 2013 to June, 2019, in 131 (8.8%) of the 1475 surgeries, the chief presenting complaint was vomiting. Hirschsprung's Disease, diaphragmatic pathologies and Infantile Hypertrophic Pyloric Stenosis were the most important surgical conditions presenting as vomiting.

Conclusion

Vomiting is a common clinical presentation in children whose etiologies range from benign conditions to potentially life threatening ones. Many surgical conditions present with emesis as initial symptom which if not recognized early can have catastrophic consequences. Hence, a high index of suspicion and a systematic approach is warranted in evaluation of a child with vomiting.

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Review Article

COPD : A Case Based Approach to the Clinician in Light of GOLD 2021

Swarup Kanta Saha[1], Atanu Chandra[2], Tarun Kumar Paria[3], Arkapravo Hati[3]

Chronic obstructive pulmonary disease (COPD) is considered to be one of the most important causes of mortality and morbidity across the globe. Many people suffering from this poorly reversible condition often have a state of chronic ill health, reduced life-span either from the disease itself or secondary to its complications. Hence proper evaluation of every COPD patients and early identification of complication are of utmost importance to prevent such calamities. This article will guide the clinicians about the approach to such patients in day to day practice.

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Key words **: Chronic obstructive pulmonary disease (COPD),**

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease which is a major cause of chronic morbidity and mortality throughout the world[1]. It is a disease state characterized by persistent limitation of airflow combined with presence of respiratory complaints, that is not completely reversible and those are either due to abnormality in the airway or alveoli. The main aetiology is thought to be related to a considerable exposure to toxic or noxious particles such as smoking, and also influenced by different host factors, combined with some of the congenital and developmental anomalies of the lung. COPD includes chronic bronchitis, emphysema and small airway disease[2]. In most of the patients, it is usually associated with or complicated by some comorbidities, which in most cases, are responsible for the worsening of the clinical course of the disease.

Editor's Comment :

- Smoking cessation is the cornerstone of therapy in patients with COPD.
- Appropriate and judicious use of inhalers should be encouraged in every COPD patient.
- Proper management of the associated comorbidities and complications along with timely management of exacerbations are of paramount importance.

Case Scenarios :

Case 1 :

A 63-year-old retired gentleman with a smoking history of one pack per day for last 33 years presented in the out-patient department (OPD) with the complaint of productive cough with greenish sputum for last several days. He also had breathlessness and fatigue. He had sought care in OPD for similar symptoms two or three times annually in the last decade. A diagnosis of COPD was made 6 years ago, and a short actingâ2-agonist (SABA) was initiated following which his symptoms got relieved and he felt much better. Recently the symptom of breathlessness is interfering with his lifestyle. Recovering from exacerbations takes longer time than before, which is often 2 weeks. During his last visit, FEV1 was 54% predicted. He is on ACE-inhibitor for hypertension for last 15 years. On examination, he was febrile; there was tachycardia (heart rate 110/min), blood pressure of 112/72mm Hg, respiratory rate of 26/min, oxygen saturation of 96% on room air.

Further Course in OPD, Outcome and Follow-up :

On careful examination, predominantly expiratory wheeze with scattered crackles were noted over both lungs. Jugular venous pressure was not raised and examinations of the cardiovascular system were within normal limits. Basic blood parameters were within normal limits, except neutrophilic leucocytosis. Patient was counselled to stop of smoking and yearly vaccination. He was treated with oral antibiotics, paracetamol. As per GOLD guidelines he was offered long acting muscarinic antagonist (LAMA) in inhaled form. He was taught about proper inhalation technique and was advised to continue SABA on as and when required basis. He was asked to revisit after 7days. During this his cough and fever subsided and his generalised condition got improved. He was asked to continue use of two inhalers as advised previously and

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

[1]MD (Internal Medicine), Senior Resident

[2]MD (Internal Medicine), DNB (Internal Medicine), MRCP (UK); Assistant Professor, Department of Internal Medicine, RG Kar Medical College and Hospital, Kolkata 700002 and Corresponding Author

[3]MBBS, Junior Resident

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remain in close follow up.

Case 2 :

A 54-year-old lady with a history of smoking presented to the emergency department with severe shortness of breath and cough. Her FEV1 was 35% (predicted) at the recent outpatient visit. She retired from her office job 5 years ago because of her breathlessness. She had quit smoking 5 years ago. Over the years she had suffered multiple exacerbations requiring antibiotics and inhaled steroids, but no hospital admission. Previously her symptoms had been controlled with bronchodilators, inhaled steroids and nebulisers as and when required. In addition to inhaled long-acting â2-agonist/ inhaled steroid combination and a long-acting anti-muscarinic, she is taking acebrophylline, N-acetyl-cysteine, and oral steroids without experiencing any beneficial effect.

Further Course in Hospital :

On examination, patient was alert, conscious and cooperative. Temperature was raised (100.8ºF). Accessory muscles of respiration were working. Patient was unable to speak in a complete sentence. Tachycardia and tachypnea were there. Chest examination revealed presence of wheezing, bronchial breath sound over mid zone of left lung. Blood investigation revealed neutrophilic leucocytosis. Chest X-ray showed hyperinflation of both lung field and a dense homogenous shadow involving mid zone of left lung. Supplemental oxygen therapy given and arterial blood gas was analysed. Hypoxemia improved with oxygen. Nebulisation with beta agonist and muscarinic antagonist was given along with parenteral antibiotics. Systemic steroids were initiated for 14 days. Following this treatment there was clinical as well as radiological improvement. She was discharged with LABA and Long Acting Muscarinic Antagonist (LAMA) in inhaler form and was advised to remain in regular follow up.

Risk Factors :

The following factors are thought to increase the risk for developing COPD :

- Tobacco smoke: Persons who smoke cigarettes on regular basis have more respiratory symptoms and pulmonary function defects and have higher chances of mortality than non-smokers. Other varieties of tobacco related products such as water pipe, cigar, and marijuana are considered as the incriminating factors for the development of COPD, besides outdoor air pollution.
- Occupational exposures
- Outdoor air pollution
- Genetic factors: Congenital deficiency of the protein alpha-1 antitrypsin (A1AD or AATD); mutation in the gene responsible for the synthesis of glutathione-S-transferase or matrix metallo-proteinase-12 is associated with deterioration of pulmonary function and increased chances of developing COPD[4].
- Age and sex: Increasing age and female gender are known risk factors
- Developmental defects of lung, chronic bronchitis and childhood infections.

Diagnosis and Clinical Assessment in COPD :

The diagnosis of COPD should be considered in any patient having shortness of breath associated with chronic cough with sputum production and history of recurrent lower respiratory tract infections, combined with presence of at least one of the known risk factors. The presence of persistent airflow limitation is suggested by a **post-bronchodilator FEV1/FVC <0.70** thus confirming the diagnosis of COPD in the background of specific symptoms and usual risk factors.[5] Presence of co-existent chronic diseases like ischemic heart disease, cardiomyopathy, metabolic syndrome, osteoporosis, depression, anxiety, and lung malignancy, should be properly evaluated and managed. The cardinal features that indicate COPD are as follows:

- **Dyspnea :** Usually progressive in nature, persistent, worse with exercise.
- **Chronic cough :** Intermittent, occasionally non-productive and associated with wheeze.
- **Chronic sputum production**
- **Presence of risk factors,** suggestive family history or history of childhood infections
- **Clinical examination findings :** In early stages of COPD, patients usually have an entirely normal physical examination. Polycythemia can be seen frequently. Tachypnea, increased activity of accessory muscles of respiration and cyanosis may indicate exacerbation. Expiratory wheeze and vesicular breath sound with prolonged expiratory phase may be present.

Investigations[6] :

- **Basic blood parameters :** Complete blood count; C-reactive protein; urea and creartinine; liver function test; blood glucose; electrocardiogram
- **Spirometry :** This is required to make the diagnosis in proper clinical context.
- **Chest imaging :** Chest X-ray features showing bullae, paucity of parenchymal findings, or hyperlucency of lung fields are suggestive of emphysema. It can also detect any alternative

diagnosis or co-existent pathology such as pneumothorax or cardiomegaly. Computed tomography (CT) thorax is not routinely performed except some special situations (to detect the complications such as lung cancer and bronchiectasis). CT scan is also needed before planning some surgical procedures like lung transplant or lung volume reduction surgery.

- **Lung volumes and diffusion capacity :** Air trapping in COPD patients leads to an increased residual volume, and with gradual worsening in airflow limitation, increment of the total lung capacity (static hyperinflation) occurs. Body plethysmography (more accurate), or helium dilution technique (less accurate) may be used to detect such changes.
- **Pulse oximetry and arterial blood gas analysis :** Oximetry may be used for evaluation of peripheral arterial-oxygen saturation of a patient and it is a reliable tool to assess any need for supplemental oxygen. It is generally used in patients with clinical signs of congestive cardiac failure or respiratory failure. Arterial blood gas analysis should be performed when the oximetry reading is <92% on room air.
- **Exercise testing and physical activity assessment :** A reduction in the self-paced walking distance or at the time of incremental exercise testing in laboratory; may be considered as a powerful objective evidence of impairment of health status and poorer prognosis; Both the unpaced 6-minute walk test and paced shuttle walk test[2,3] may be used. Laboratory testing using treadmill ergometry may help in diagnosing co-existent cardiac ailments.
- **Screening of Alpha-1 Antitrypsin Deficiency (AATD) :** The WHO recommends screening in areas with high prevalence of AATD and when the usual risk factors are absent.

Differential diagnosis of COPD (Table 1) :

Table 1 — *The differential diagnosis of COPD*[5]

Diagnosis	Suggestive feature
Asthma	Early age of onset, symptoms worse at night/early morning, seasonal variation of symptoms, history of allergy, rhinitis, eczema; and family history of asthma
Congestive cardiac failure	Orthopnea, pedal swelling, raised JVP, third heart sound on examination, cardiomegaly in chest imaging, pulmonary edema
Tuberculosis	Constitutional symptoms like weight loss, anorexia, night sweats; Chest X-ray showing patchy opacity or cavitary lesions, and microbiological evidence.
Bronchiectasis	Large volume of purulent sputum, bacterial infections common, CT chest shows bronchial dilatation, bronchial wall thickening.

Airflow Limitation Severity :

The classification of airflow limitation severity in COPD with specific spirometric cut-off has been depicted in Table 2[5].

Table 2 — *Spirometry classification of COPD*

In patients with FEV1/FVC < 0.7		
CATEGORY	SEVERITY	SPIROMETRY (% predicted)
GOLD-1	Mild	FEV1 ≥ 80%
GOLD-2	Moderate	50% ≤ FEV1 < 80%
GOLD-3	Severe	30% ≤ FEV1 < 50%
GOLD-4	Very severe	FEV1 < 30%

Assessment of COPD :

Initially COPD was thought to be a disease mainly characterized by breathlessness. A simple standardized measurement of breathlessness such as the Modified Medical Research Council (MMRC) Questionnaire is commonly used for assessment of respiratory symptoms. However, this is well-recognized fact that COPD has a greater impact on the quality of life of a patient beyond dyspnea. Moreover, the COPD Assessment Test (CAT) and the COPD Control Questionnaire (CCQ) can be used to assess such patients in a comprehensive manner.

Combined COPD Assessment :

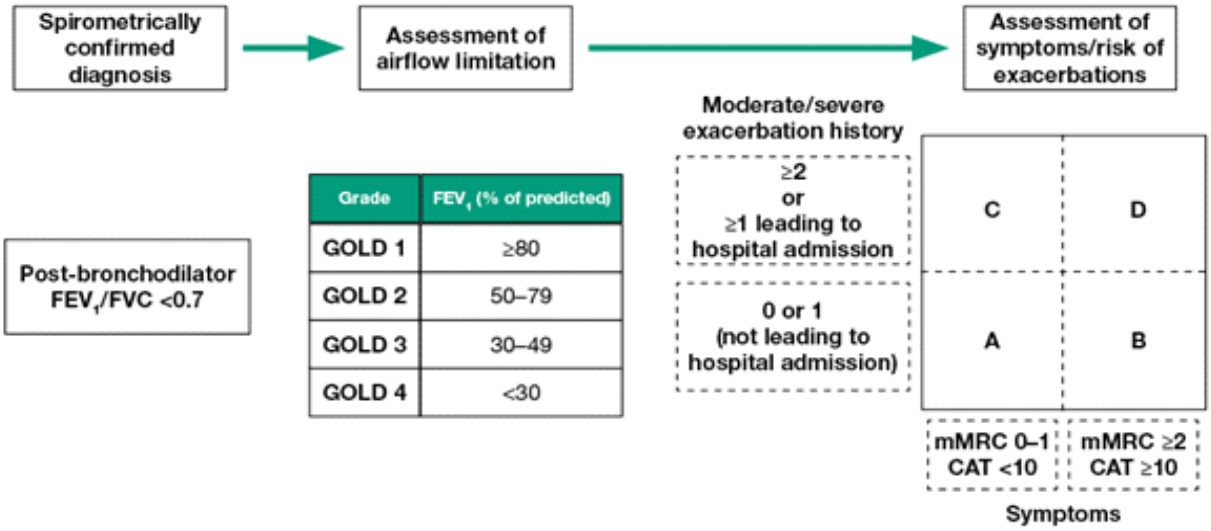
A combination of spirometry, along with patient symptoms and exacerbations history, may be used as an assessment tool. It remains vital not only for the diagnosis but also for prognostication and consideration of alternative therapeutic approaches. This new approach for assessment has been depicted in Fig 1.

Management :

- **Initial management :**

(1) Smoking cessation: It is the cornerstone in management of COPD. Pharmacotherapy combined with the nicotine replacement enhances a long duration of abstinence. Legal actions against smoking, and proper counselling when delivered by skilled healthcare professionals, have been seen to improve quit rates. However, the safety and efficacy of e-cigarettes as an aid for smoking cessation is quite uncertain at present.

(2) Vaccination: Seasonal Influenza vaccination has been seen to significant reduce recurrent hospitalizations, lower respiratory tract



FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; mMRC=modified Medical Research Council dyspnoea questionaire; CAT=COPD assessment test.

Fig 1 — Assessment in a COPD patient

infections and mortality. Pneumococcal vaccination has also been proved to be beneficial. Use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) has a proven role in reduction of the risk of community acquired pneumonia in patients with COPD of <65 years of age and FEV1 <40% predicted and in presence of concomitant chronic diseases. In case of adults e"65 years, 13-valent conjugated pneumococcal vaccine (PCV13) has proved to be efficacious in reducing the chances of severe pneumococcal disease. Tdap vaccination (dTaP/dTPa) has been recommended by the CDC in patients of COPD to protect them against tetanus, pertussis, and diphtheria, only applicable to those who had not taken this in adolescence[7].

- **Pharmacotherapy :**

(1) Bronchodilators : Inhaled bronchodilators are key to symptomatic management in COPD patients and given on regular basis. Regular and as needed short acting beta agonist (SABA) and short acting muscarinic antagonist (SAMA) are seen to be associated with symptomatic improvement along with an increase in FEV1. Long acting beta agonist (LABA) and long acting muscarinic antagonist (LAMA) have a significant role in improvement of shortness of breath, lung function, general health status, and reduction in exacerbation rates.[8] Combined treatment with LABA and LAMA has been associated with a significant symptomatic improvement along with increase in FEV1 and reducing exacerbations, when compared to the monotherapy. Currently available LABA- formoterol, salmeterol and indacaterol; SAMA- ipratropium bromide and oxitropium bromide; LAMA- tiotropium, aclidinium and glycopyrronium.

(2) Anti inflammatory therapy :

- **Inhaled corticosteroid (ICS) :** ICS when combined with LABA, is seen to be more efficient than individual treatment in improving health status, lung function and reduction in the frequency of exacerbations. Triple inhaled therapy in the form of LABA/LAMA/ICS significantly improves overall lung function, quality of life and reduces exacerbation in comparison to the individual components.
- **Oral glucocorticoids :** Long term use of oral steroids has many adverse effects with no proven benefits except in exacerbation.
- **PDE4 inhibitors :** In patients with severe COPD with history of exacerbation and chronic bronchitis, PDE 4 inhibitor may improve lung function and exacerbations.
- **Antibiotics :** Evidence suggests long term Azithromycin therapy reduces exacerbation but it is associated with increasing bacterial resistence and hearing impairments.
- **Mucoregulators and antioxidants :** Mucolytics commonly used such as N-acetyl-cysteine, carbo-cysteine reduces exacerbation in selected patients.

(3) Oxygen therapy in stable COPD : Long term oxygen therapy (LTOT) has a survival benefit in patients with severe resting hypoxemia and routine supplemental oxygen therapy has no proven value in stable COPD patients without severe resting hypoxemia. Supplemental oxygen should be titrated according to the patient's clinical status and arterial blood gas

parameters to achieve a target saturation of 88-92%.

(4) Interventional therapies in COPD : Lung volume reduction surgery, bullectomy, transplantation, bronchoscopic interventions such as endobronchial valve, lung coils, vapour ablation

The treatment algorithm of stable COPD is depicted in Figs 2 and 3.

Management of Exacerbation :

An exacerbation of COPD is defined as sudden deterioration of existing respiratory symptoms that mandates additional therapy. As the symptoms are mostly non-specific to COPD, therefore relevant differential diagnoses should be kept in mind (Table 3).

COPD may be exacerbated by several factors with respiratory tract infection being the most common incriminating factor. The goal for treatment of COPD exacerbation is to manage the current event appropriately and aggressively, and to prevent such episodes in future.

Management of serious but not life threatening exacerbation:

- After initial assessment administer supplemental oxygen, obtain serial arterial and venous blood gas, pulse oxymetry measurement.
- Bronchodilators : For the treatment of acute exacerbation, short-acting inhaled beta2-agonists (SABA), with or without short-acting anticholinergics (SAMA) are preferred as initial bronchodilators.

♦ Increase dose and or frequency

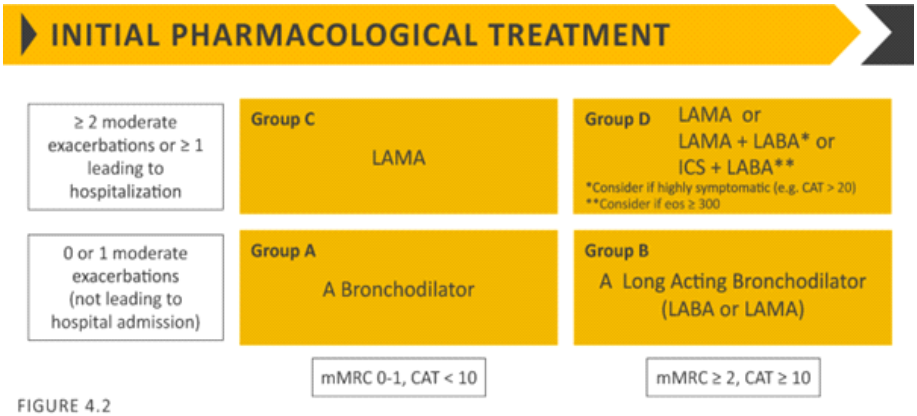


Fig 2 — Initial pharmacological treatment of stable COPD (adapted from GOLD 2021)
Abbreviations : EOS: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

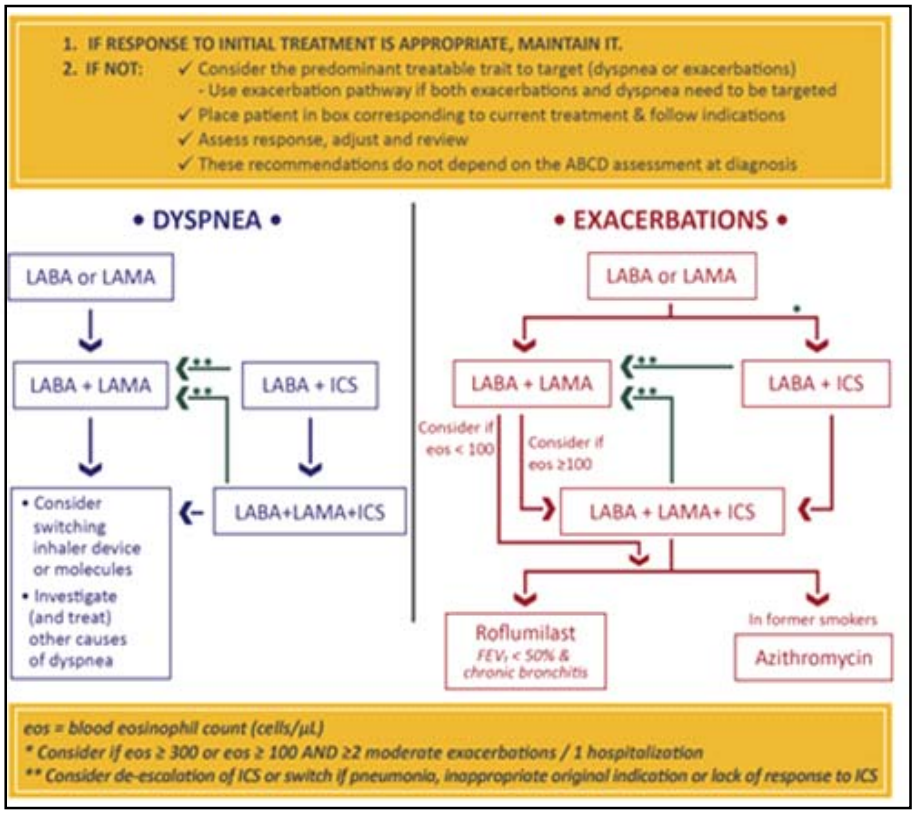


Fig 3 — Follow-up pharmacological treatment of stable COPD (adapted from GOLD 2021)

Table 3 — *Differentials of exacerbation*

Clinical Conditions	Relevant investigation
Pneumonia	Chest Xray, CRP, Pro-calcitonin
Pleural effusion	Chest X-ray or ultrasound
Pneumothorax	Chest Xray or CT chest
Pulmonary embolism	D-dimer and or Doppler lower limb; Chest CT
Pulmonary edema (Cardiogenic)	ECG, cardiac enzymes
Arrythmias (Atrial fibrillation or flutter)	ECG

of short acting bronchodilators

- ♦ Combine short acting beta2 agonist and anticholinergics
- ♦ Consider long acting bronchodilators when patients are stable
- ♦ Use spacers or air driven nebulisers when possible

• Oral corticosteroids: Systemic corticosteroid has a proven benefit on lung function (FEV1), oxygenation and reduction of hospital stay. The usual duration should not exceed 5-7 days.

• Consider oral antibiotics if bacterial infection is present. Antibiotics, when indicated, reduce the hospital stay, fasten recovery, reduce early relapse, and treatment failure. Duration of therapy should not exceed 5-7 days.

• Consider non invasive ventilation (NIV): It should be considered as the first mode of ventilation in patients of COPD with acute respiratory failure in absence of any absolute contraindication.

• In every case : Careful monitoring of the fluid balance. Low molecular weight heparin should be used for thrombo-prophylaxis

• Prompt identification and treatment of co-existing conditions such as heart failure, pulmonary embolism etc.

• Early initiation of maintenance therapy with long-acting bronchodilators (if possible before hospital discharge).

• Appropriate measures for prevention of exacerbation.

Indication for Invasive Ventilation :

- • Inability to tolerate no-invasive ventilation
- • In patients of post-respiratory/cardiac arrest
- • Altered sensorium, restlessness or agitation which cannot be adequately controlled with sedatives
- • Persistent vomiting or aspiration
- • Presence of hemodynamic instability without any response to fluids/vasopressors
- • Severe supraventricular/ventricular arrhythmia

COPD and Comorbidities[9]:

COPD is often associated with some chronic diseases (comorbidities) which may be significantly related to the outcome, health status, and prognosis of such patients. Management of COPD patients with chronic diseases is no different from the usual protocol, however these comorbidities must be treated simultaneously. Cardiovascular diseases comprises major portion of all comorbidities in COPD. Lung cancer is not very uncommon in patients of COPD and it is associated with increase in adverse outcome and mortality. Osteoporosis and psychiatric disorders such as depression and anxiety are common and often under-diagnosed, and their presence is often associated with poorer prognosis. Gastroesophageal reflux (GERD) is a common precipitating factor for exacerbations.

COVID -19 and COPD :

Stable COPD patients having a new respiratory symptom or worsening of the existing symptoms, presence of fever, or any COVID-19 related symptoms, should always be evaluated promptly to exclude SARS-CoV-2, irrespective of the severity of symptoms. Restriction of spirometry should be considered during the rapid surge in COVID-19 cases in the community. It should only be performed in selected cases for diagnosis, and/or assessment of lung function needed before elective surgery or interventional procedures. Patient's education regarding the COVID-19 and its management is of paramount importance.

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Review Article

SARS-COV-2 Vaccines : A Systematic Review

Rajat Varshney[1], Shelly Dutta[2], Anshuman Srivastava[2], Amitesh Aggarwal[3], Subhash Giri[4], Ashish Goel[5]

COVID-19 has emerged as a major pandemic in recent times which has caused great distress worldwide and resulted in high mortality. As a result, substantial efforts are being made into developing effective treatment and vaccines against the virus. Currently, numerous vaccines developed against COVID-19 have got emergency approval in various countries and many others are still in clinical development. This review provides an overview of experimental and clinical data of common vaccines in use and highlight potential safety issues with their use. Furthermore, we also highlight current data about the safety and efficacy of vaccines among vulnerable groups of our society.

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Key words **: COVID-19 Vaccine, RNA Vaccine, Covaxin, Comparison of COVID Vaccine, Coronavirus Vaccine.**

SARS-COV-2 is an enveloped, spherical RNA virus. The virus contains a helical nucleocapsid which is enclosed bya viral membrane consisting of the following 3 proteins : (i) transmembrane (M) glycoprotein (ii) Spike (S) glycoprotein (iii) envelope (E) protein[1,2]. The spike protein binds to the receptor on host cell membrane and aids in entry of the viral genome into the host cell. It contains two subunits, membrane-proximal S2 subunit and membrane-distal S1 subunit. Receptor binding domain (RBD) present on S1 subunit binds to ACE2 receptors present on the host cell membrane. Binding of S1 subunit leads to change in configuration of S2 subunit that is responsible for membrane fusion and viral entry into the cell[3,4]. M and E proteins are small proteins that are embedded in the viral membrane and are responsible for structure and infectivity respectively[4].

Immunogenicity of Viral Proteins :

"Immunogenicity is the ability of a substance to induce a cellular or humoral immune response while antigenicity is the ability to be specifically recognized by the antibodies generated as a result of the immune response to the given substance" (Ilinskaya & Dobrovolskaia, 2016)[5]. SARS-COV-2 M and E proteins have poor immunogenicity due to their small size. N protein contains immunogenic properties butanti-N immune sera have no protective role against SARS cov infection probably due to being a non-membrane protein. S protein being immunogenic and reported a protective role of anti-S anti sera against covid infection, is the major protein target of COVID vaccines[4].

Editor's Comment :

- Spike protein(S) is the main immunogenic protein in SARS-COV-2 and is the major target of all covid vaccines.
- SARS COV 2 vaccines are based on various platforms. Commonly used platform are: mRNA based, DNA based, protein subunit based, Inactivated virus based, viral vector based.
- All vaccines were found to be effective in elderly with lower frequency of adverse events as compared to general population.
- There is a paucity of data in vulnerable groups such as children, pregnant women. Some studies are underway and further studies are needed for this section of society.

Vaccination Strategies :

As of 23 March as per the WHO COVID vaccine tracker, 83 vaccines are in the clinical phase while 184 vaccines being in the pre-clinical phase[6]. These vaccines are based on many platforms with S protein being a target antigen. Common types of vaccines are:

- RNA based vaccine
- Viral Vector based vaccine
- Inactivated Virus based vaccine
- Protein subunit based vaccine
- DNA based vaccine

RNA based Vaccines: mRNA encoding Spike glycoprotein(S) serves as the basis of these vaccines. These are formulated in lipid nanoparticle which protects it against enzymatic degradation. These vaccines are administered intramuscularly. Macrophages and antigen presenting cells (APCs) present near the administered vaccine engulf the mRNA. The mRNA within the cells encodes spike glycoprotein which is presented on the membrane by

Department of Medicine, UCMS and GTB Hospital, Delhi 110095
[1]MBBS, Junior Resident
[2]MD, Assistant Professor
[3]MD, FICP, Professor
[4]MD, Director, Professor
[5]MD MPH, Professor and Corresponding Author

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APCs and further leads to humoral and cellular immune response[7]. Pfizer-Biontech COVID-19 Vaccine and Moderna COVID-19 vaccine currently in use are based on this platform.

Viral Vector based Vaccine:Some genetically altered non-pathogenic viruses are used as vectors to carry antigens of disease-causing pathogen. These non-pathogenic viruses express antigen of disease causing pathogen on their membrane and elicit an immune response against the pathogen. Many vaccines use recombinant adenovirus containing DNA that encodes spike protein of SARS-COV-2. Recombinant Ad vector induces a robust immune response (specifically involving CTL after infecting host APCs and inducing Spike glycoprotein) due to their high transduction efficiency, transgene expression and broad gamut of viral tropism[8]. Oxford Astrazaneca Ch AdOx1 nCoV- 19 Corona Virus Vaccine, Janssen Ad26. COV2.S Vaccine, Sputnik V are based on this platform.

Inactivated Virus based Vaccine:In these types of vaccines, inactivated whole SARS-COV-2 virus is used. These inactivated viruses can produce both structural and non-structural proteins thus conferring broader antibody and T-cell response[4]. Covaxin developed by Bharat Biotech is based on this platform.

Protein Subunit based Vaccine:A subunit vaccine contains a specific viral antigenic fragment that is produced by recombinant technology and does not contain any component of infectious virus. This eliminates any concerns of incomplete inactivation of the virus as in live-attenuated vaccines. S protein is mainly used in the development of subunit vaccines. Various vaccines containing it are in clinical and preclinical developmental stage. These may contain the whole S protein or merely the S1 sub unit or receptor binding domain of S1 subunit[9]. N- terminal domain of S1 subunit and S2 subunit is less immunogenic thereby a less favourable target for vaccine development[10]. Spike protein exists in two conformational states, pre-fusion and postfusion. For the production of protective immune response, the antigen must remain in its pre fusion state[11]. Novavax, pittcovaxx vaccines are based on this platform.

DNA Vaccines : These vaccines contain DNA particles that encode spike protein. DNA after being injected subcutaneously gets transfected in APCs. These APCs express antigen coded by DNA after loading on MHC1 and MHC2. These APCs can migrate to draining lymph nodes and produces a robust immune response after priming CD8+ and CD4+ immune cells[12]. ZyCov-D, INO-4800 are DNA based vaccines currently in clinical development.

Efficacy of Vaccines :

Vaccine efficacy is the percent reduction in the incidence of symptomatic disease in a group who received a vaccination compared to those who did not in a clinical trial. It is calculated as 100 × [1 – (the attack rate with vaccine ÷ the attack rate with placebo)]. A vaccine having an efficacy of 90% does not mean that 90% of people who got the vaccine will not get the disease. It means that if a cumulative disease attack rate is 1% in the general population, it will be reduced to 0.1% in vaccinated group[13].

Antibody Dependent Enhancement (ADE) Response due to COVID Vaccines :

ADE response is antibody dependent enhancement that could occur due to formation of non-neutralizing antibodies against the virus and can paradoxically produce enhanced response of the virus. None of the vaccines have so far shown to develop ADE response. The RBD of the virus can produce these neutralizing antibodies, although the other regions are protected by glycosylation. This prevents the generation of non - neutralizing antibodies that may exhibit ADE[14].

Vulnerable Groups :

Children —

As of now, most of the studies conducted to determine efficacy and adverse events of vaccines are done in those with age >18 years. Only Pfizer's COVID vaccine was studied in those with age >16 years and is approved for use in those with age >16 years[15-17].

Pregnant Women —

There is paucity of data regarding the safety and efficacy of these vaccines in pregnant and lactating females. This can be attributed to most trials excluding this population from their study. Clinical trials regarding this are underway. Data of those who became pregnant after receiving the vaccine is also being assessed by the manufacturers[21]. Developmental and toxicology study which looks at the adverse effect of a drug on pregnancy in animal model has been conducted for Moderna vaccine only and it showed no adverse effect on pregnancy[22]. A report on developmental and toxicology study conducted by Pfizer–BioNTech is expected to be sent to FDA in near future[21].

Elderly —

Notably, the older adults form the major chunk of the population that has been affected gravely by COVID-19 causing higher morbidity and mortality in them[23]. Developing a safe and effective vaccine for this group was definitely the need of the hour. All vaccines were effective in elderly individuals. A lower frequency of adverse reactions was noted in elderly as compared

Comparison of Common Vaccines :

	Pfizer(15)	**Moderna**(16)	**Covishield**(17,18) **Astra Zeneca**	**Covaxin*** (19) **Bharat Biotech**	**J & J***(20)
Efficacy	94.6%, 7 days after 2nd dose	94.1 %, 14 days after 2nd dose	66.7%, 14 days after 2nd dose	Interim vaccine efficacy 81%	66%, 28 days after vaccination
Type	mRNA	mRNA	Genetically altered Adenoviral vector carrying SARS CoV-2 DNA for spike protein	Inactivated virus providing structural and non-structural protein for broader response	
No of Inj	2	2	2	2	1
Storage	-90°C to -60°C	-25°C to -15°C	2°C to 8°C	2°C to 8°C	2°C to 8°C
Age	16 and above	18 and above	18 and above	18 and above	18 and above
Dose	0.3ml 3 week apart IM	0.5ml 28 days apart IM	0.5ml 4-12 week apart IM	0.5 ml 28 days apart IM	0.5 ml single dose IM
Contraindications:	•allergic to the lipid nanoparticles	•allergic to the lipid nanoparticles	•allergic reaction after a previous dose of this •allergic reaction to any ingredient of this vaccine	•Have any history of allergies. • Have fever. • Have a bleeding disorder or are on a blood thinner. • Are immune-compromised or are on a medicine that affects your immune system • Are pregnant. • Are breastfeeding. • Have received another COVID-19 vaccine. • Any other serious health related issues, as determined by the Vaccinator/Offer supervising	•hypersensitivity to vaccine component
Side effects	•Injection site pain (83%) •erythema (5%) •injection site swelling (6%) •headache (42%) •fatigue (47%) • fever (4%) •lymphadenopathy (0.3%)	•Injection site pain (91.6%) •injection site erythema •injection site swelling •headache (63%) •fatigue (68.5%) • fever •myalgia (59.6%) •nausea •Lymphadenopathy (1.1%) •Hypersensitivity reaction (1.5%) •Bell's palsy(<0.5%)	Very Common (>1 in 10 people) • tenderness, pain, warmth, • redness, itching, swelling or •bruising where the injection is given •Joint/Muscle ache •Fatigue •Fever •Headache •Nausea Common(up to 1 in 10) Lump at the injection site Flu like symptoms Uncommon (1 in 100) Dizziness Decreased appetite Abdominal Pain Enlarged Lymph Node Excessive sweating/itchy skin/ rash	• Injection site pain • Injection site swelling • Injection site redness • Injection site itching • Body ache • Headache • Fever • Malaise • Rashes • Nausea • Vomiting	•Injection site pain (48.6%) •headache (38.9%) •fatigue (38.2%) •myalgia (33.2%) •nausea • fever •injection site erythema •injection site swelling •Hypersensitivity reaction

*phase 3 data currently not available

to the general population.This may be due to the lower ability to mount an acute inflammatory response with increasing age[24]. Vaccine efficacy in the elderly group given covishield could not be assessed due to insufficient data[17]. Immunogenicity in elderly receiving covishield, as assessed by anti-IgG against spike protein, was robust and comparable to that in general population[25]. Pfizer and Moderna COVID vaccines have reported efficacy of 94.7% and 86.4% in individuals aged 65 and above.

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Case Report

Situs Inversus Totalis with Atrial Septal Defect : A Rare Association

Mahesh Dave[1], Puneet Patel[2], Saurabh Jain[2], Aniruddha Burli[2]

Situs inversus totalis is the complete inversion of position of the thoracic and abdominal viscera. It may be isolated or associated with malformations, especially cardiac and/or alimentary. Usually it remains asymptomatic and is discovered as an incidental finding in adulthood, but sometimes it may be discovered during infancy itself due to associated anomalies. We report a 19-year-old male found to have situs inversus totalis in association with Atrial Septal defect (ASD) while presenting to a medical OPD. This incidental finding situs inversus totalis in association with Atrial Septal defect (ASD) was detected by physical examination and was confirmed later by echocardiogram and other radiological studies. This report emphasizes the importance of complete physical examination with special reference to patients presenting with dextrocardia/situs inversus. [*J Indian Med Assoc* 2021; **119(6):** 60-1]

Key words **: Situs inversus totalis, Atrial septal defect, Congenital heart disease.**

Situs inversus totalis refers to a right-sided location of the heart within the thoracic cavity with complete mirror imaging of abdominal viscera. It is a primary manifestation of the abnormal lateralisation of the embryonic left-right axis during early development[1]. While its true incidence remains largely unknown, estimates range from 1 in 8,000 to 25,000 live births[2]. Chest radiograph, Ultrasonography and an electrocardiogram are enough to make a diagnosis of dextrocardia, while more recent imaging modalities like echocardiography and magnetic resonance imaging confirms the diagnosis[3]. Situs inversus totalis is usually associated with variable congenital anomalies which include primary ciliary dyskinesia (Kartageners syndrome) and Cardiac defects[4]. The common cardiac anomalies seen in situs inversus totalis include Transposition of great vessels (3-5%), Atrio-ventricular discordance and right sided aortic arch. Atrial Septal Defect (ASD) is very rare congenital anomaly associated with situs inversus totalis. Hence, we report this case of Situs inversus totalis with Atrial Septal Defect (ASD).

Editor's Comment :

- Situs inversus totalis is a rare condition characterized by completely reverse positioning of heart and abdominal viscera.
- Detection of prior cardiac anomalies is very important as invasive cardiac procedures, if needed, are very challenging in such patients.

Case Report

A 19 years old male came to medical OPD with complains of chest pain and shortness of breath on & off for past five months. Chest Pain was non-radiating, dull aching type, increased by exertion and was not associated with palpitations, diaphoresis, dizziness or loss of consciousness. He had no history of orthopnoea, Paroxysmal Nocturnal Dyspnea (PND) and bilateral swelling of lower limbs. Past history revealed recurrent episodes of upper respiratory tract infections since childhood. On general physical examination, Patient had pallor with no clubbing, cyanosis and pedal oedema. His vitals were normal. Cardio Vascular System (CVS) examination revealed apex beat on right side of chest, 10.5 cm lateral to mid sternal line in 5th Inter coastal space with normal character. On auscultation wide fixed splitting of second heart sound at right upper sternal border (no variation with respiration) was noted. Rest was normal. Abdominal examination showed no organomegaly, but on percussion, liver dullness was found on the left side upper abdomen. So clinically, situs inversus totalis with ASD diagnosis was suspected and the patient was subjected to further extensive workup. His all routine investigations which include Renal Function Tests (RFT), Liver Function Tests (LFT) and urine examination were within normal limits except for hemogram which showed Anaemia with haemoglobin 8.4gm%. X-ray Chest donewas showing heart on the right side with apex pointed towards the right side. The aortic arch was on the left side.The left hemidiaphragm was raised and the gastric bubble was on the right side.Abdominal ultrasound revealed that the liver and gallbladder were on the left side whereas the spleen was on the right side suggestive of situs inversus. His Echocardiography done and were suggestive of dextrocardia with Inferior venacava, superior venacava draining into left sided right atrium, pulmonary veins draining into right sided left atrium, AV/VA concordance, great arteries relation normal, ostium secundum type of atrial septal defect of 2.5 mm in size, with shunt from left atrium to right atrium, mild Tricuspid Regurgitation (TR) with dilated right atrium and right ventricle and intact interventricular septum.

Discussion

Situs inversus totalis is a rare congenital anomaly reported to occur in 1 in 8000 to 1 in 25,000 patients[5]. On review of literature the incidence approximately appears

Department of General Medicine, RNT Medical College, Udaipur, Rajasthan 313001

[1]MD, FICP, FRCP, Senior Professor & Ex-Head and Corresponding Author

[2]MD, Junior Resident

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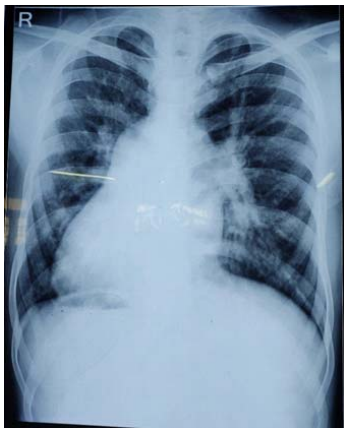

Fig 1 — X ray chest PA view showing dextrocardia with fundic gas shadow on right side

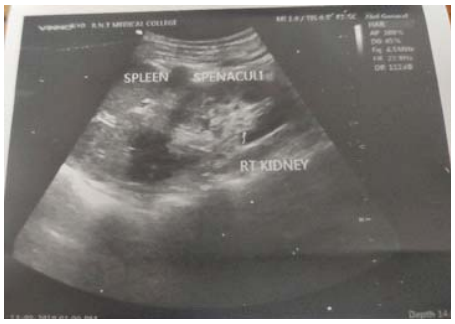

Fig 2 — USG Abdomen showing situs inversus

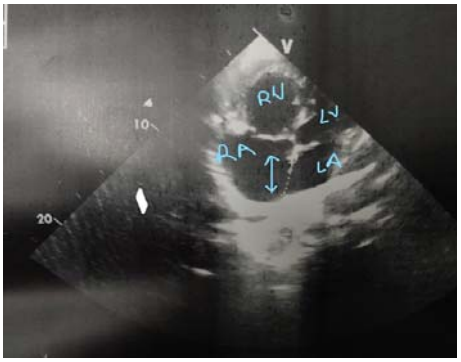

Fig 3 — Echocardiography (4 chamber view) showing Ostium secundum type of ASD. The defect is showed with dotted line measuring 2.5mm

to be 1:10,000 adults and although it appears to be genetically determined the exact mode of inheritance is not clear[6]. The male-to-female incidence is 1:1. The arrangements of the position of the abdominal viscera in dextrocardia may be normal (situs solitus), reversed (situs inversus totalis), or indeterminate (situs ambiguous or isomerism) in 32 to 35%, 35 to 39%, and 26 to 28% of cases, respectively.The interatrial septum plane is oblique in cases of laevocardia, with the left atrium more posterior than the right atrium. In dextrocardia, the interatrial septum is directed anteriorly and to the right, with the morphologic right atrium situated to the right and slightly posteriorly, and the morphologic left atrium to the left and slightly anteriorly[7].

The diagnosis of dextrocardia by foetal echocardiogram has estimated an overall incidence of between 0.22% and0.84% in pregnant women referred for pre-natal cardiac ultrasound. A large proportion of these foetuses have associated Coronary Heart Disease (CHD). The prevalence of dextrocardia in an adult population is unknown. With the advancement of new surgical techniques to correct previously fatal cardiac abnormalities, patients with dextrocardia and CHD surviving to birth are increasingly surviving into adulthood[8].

Dextrocardia with a normal abdominal situs is often associated with congenital cardiac anomalies take transposition of the great vessels and Atrial Septal Defects (ASDs) 6 and Ventricular Septal Defects (VSDs) 7 in 90 to 95% of cases, However, dextrocardia with situs inversus is associated with a lower incidence of congenital heart disease[9]. Associated Cardiac anomalies described in patients of dextrocardia with situs inversus are: VSDs, ASDs, complete AV canal defect, pulmonary atresia, TOF and double outlet right ventricle. Kulkarni and Inamdar reported a case of large peri membranous VSD associated with dextrocardia and situs inversus.[10]Situs inversus totalis may be associated with other congenital anomalies such as duodenal atresia, asplenium, multiple spleens, ectopic kidney, horseshoe kidney, and various pulmonary and vascular abnormalities[11]. Situs inversus totalis without other congenital anomalies have normal life expectancy. The recognition of Situs inversus totalis is also important for preventing surgical errors that result from the failure to recognize reversed anatomy. Cardiac interventions like transcatheter closure of Patent Ductus Arteriosus (PDA), ASD, VSD and procedures like Balloon Mitral Valvotomy (BMV) also pose orientation problems for the operator.

Conclusion

Situs inversus totalis remains a rare finding in adults, even in a highly select group of patients with known congenital heart disease. Complete diagnostic work up of suspected cases by various imaging modalities is required. Doctors should encourage routine physical examination which could help identify this anomaly, preventing wrong diagnosis and possibly death due to delay in management.

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Case Report

Type 1 Diabetes with Nodding Syndrome

Meet Shah[1], Banshi Saboo[2]

Nodding syndrome is an epileptiform encephalopathy- a type of neurodegenerative disorder. It's commonly seen in certain parts of African countries (Sudan, Tanzania) where children between 3 to 18 years of age are affected. It's characterized by head nodding, stunted growth, delayed puberty, seizures, endocrine dysfunction, cognitive decline & behavioural problems. Exact etiology is not known but potential reasons could be: nematode infection, malnutrition. MRI brain reveals diffuse atrophy of cerebral & cerebellar areas while EEG shows generalised spike wave or mutifocal spike wave discharges. Treatment includes antiepileptic therapy, nutritional rehabilitation, psychiatric counselling and physiotherapy. Here, we want to report the first case of Type 1 Diabetes who presented with Nodding syndrome from India.

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Key words **: Type 1 diabetes, Nodding syndrome, Cerebral atrophy.**

Case Report

18 years old female patient was referred to our clinic for management of uncontrolled sugar with multiple episodes of hypoglycaemia. She also had complained of involuntary movements of head as well as both upper limbs. As patient was not much responsive to our questions so further history was given by her parents. First head nodding got started about one & half year before. It was gradual in onset with few episodes of head nodding per minute but since last 4 months it was markedly increased in frequency. She was having vertical & sometimes horizontal head nodding episodes 25-30 per minute which disappeared during sleep. She also had coarse movements in both hands since last 1 year. They were asymmetrical in nature (Affecting right hand more than left). No cranial nerve palsy was noted. No history of fever or convulsions, chronic illness (except Type 1 Diabetes) observed till present.

Examinations — On Examination, she had lean & thin built up. Her height was stunted. Marked wasting was noted in all four limbs. She had no menses & had all features of delayed puberty. She used to keep herself isolated except when she wanted any kind of help or when she wanted to eat, she used to speak few words. Her both pupils were reactive to light. Deep tendon reflexes were not elicitable. Bilateral extensor plantar response was noted. Cog wheel rigidity was noted in all four limbs.

In past she had similar complain about 4 years back. At that time only head nodding was there which persisted for about 1 year for which they consulted physician & it disappeared after 1 year. Due to cognitive decline,she was dropped out from school after 7th class.

Editor's Comment :

- Nodding syndrome (NS) can be observed even in India. We need to identify more such cases where undernutrition is quite prevalent.
- Type 1 Diabetes with Nodding syndrome: First case reported from India.
- By early identification, we can manage them in better way as they need multimodal approach which helps to improve quality of life & empower them to live independently.

Her birth weight was around 1.8 Kg. She was a preterm baby delivered at 7 months pregnancy by normal vaginal delivery. She had no other siblings.She remained markedly undernourished during her childhood.

Regarding diabetic history, she was first diagnosed as type 1 diabetic when she was 10 years of age. She had very poor control of diabetes which might be due to lack of education, financial constrain & cognitive decline. She got admitted for Diabetic Ketoacidosis (DKA) four times in past 3 years. Currently, she was on premix insulin (30/70) & she had HbA1c of 10.5%. She also had frequent episodes of hypoglycaemia on premix insulin.

Her height was 142 cm, weight: 31.3 Kg with Body Mass Index (BMI) of 15.5 Kg/m^2. Vitals were within normal limits.

Blood investigations were done. Her HbA1c was 10.6% (<7%- well controlled) with c peptide of 0.2 ng/ml (0.92–3.73 ng/mL). All other reports were within normal limits. HIV serology was negative.

Fundus was suggestive of mild Non-proliferative Diabetic Retinopathy (NPDR) otherwise rest other findings were normal. EEG Report was found to be normal. MRI Brain revealed marked cerebral atrophic changes with prominent sulcal space and ventricular system. As compared to previous MRI brain which was done 1 year before, there was mild increase in atrophic changes (Figs 1-3).

[1]MD (Medicine), Consultant Diabetologist, Dia Care - Diabetes Hormone Clinic, Ahmedabad 380015 and Corresponding Author

[2]MD (Medicine), PhD (Diabetes), Msc Endo(UK), FACE, FACP, FICN, FRCP, Chief Diabetelogist & Chairman, Dia Care - Diabetes Hormone Clinic, Ahmedabad 380015

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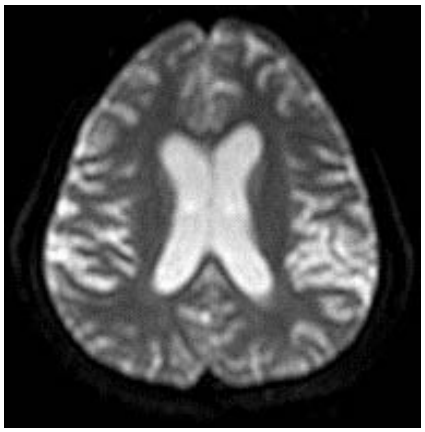

Fig 1

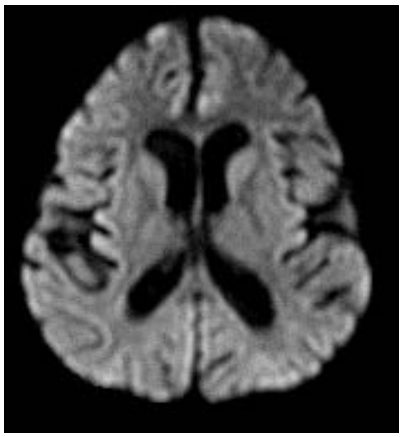

Fig 2

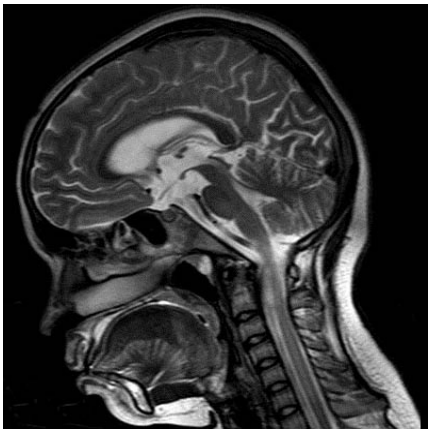

Fig 3

Figs 1-3 — All MRI images are showing features of cerebral atrophy

She was diagnosed as confirm case of Nodding syndrome based upon clinical features & brain imaging. After consulting neurophysician, she was started on Tablet valproate 287 mg, propranolol 40 mg & topiramate 25 mg (All three tablet to be taken once a day). Other supportive management including physiotherapy, psychiatric counselling &nutritional rehabilitation was made. At 3 months follow up, her head nodding & rigidity of limbs improved but it was not completely resolved. She was now involved more with outer environment & used to help her parents in household work. Overall, her psychiatrics features also improved & she seemed to be in better position than before treatment.

For diabetes, we stopped premix insulin & started her on basal bolus regimen. She was treated with regular human insulin 6 units before each meal & glargine 12 units at 10 pm. Self monitoring of blood glucose was explained to her parents. Dietary recall was made & right insulin injection technique was explained. She was in touch with us over teleconsultation & her insulin units were titrated as per her sugar readings. At 3 months follow up, her sugar was relatively controlled with HbA1c of 7.8% & no hypoglycaemia further. She also gained weight of about 4 kg.

Discussion

Nodding syndrome (NS) is a type of neuro-degenerative disease characterised by epileptic encephalopathy. Certain parts of African countries where there is high risk of malaria & onchocerca volvulus (River blindness) transmission like Tanzania, Southern Sudan & Uganda are significantly affected with this syndrome[1].

Etiology

Exact etiology is not known but poverty & malnourishment are frequent association. As compared to normal individuals, increased rate of systemic infection is found with O. volvulus although Polymerase Chain Reaction (PCR) testing of brain & CSF fluid has been found to be negative which excludes Central Nervous System (CNS) infection. There is possible chance of molecular mimicry to antigen “leiomodin-1” which is considered to be present on O.voluvulus[2,3].

Case Definitions[4] (Table 1)

Table 1

Case Category	Criteria	
Suspected case	Head nodding developed in normal subject	
Probable case Requires 2 major & 1 minor criteria	Suspected case with Major criteria: - Onset of nodding between 3 to 18 years Age - Frequency of nodding 5–20 per minute.	one of the following minor criteria:- - Delayed puberty - Psychiatric symptoms. - Other neurological issues* - Nodding Triggered by food/cold - Stunted growth - Clustering in space or time with similar cases
Confirmed case	Probable case with documentation of nodding episode that is: - Observed by expert Medical person, or - Videotaped, or - EEG/EMG	

*Other neurologic abnormalities include cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities.

Clinical presentation

Most common age group affected is of 3 to 18 years. Peak incidence is around 10 years of age. Peculiar feature of this disease is head nodding with frequency of 5-20/min. Studies done on NS revealed that there are five stages[5] (Table 2).

Nodding can precede or even accompany stage of seizures. Evaluation of stages is variable & it may differ in individual cases. NS can be considered a proconvulsive stage as nodding gets triggered by cold or food[6].

Investigation

EEG: There is no uniformity in pattern of EEG. Interictal epileptic discharges can be of (1) generalised slow spike-wave (2) Multifocal spike- wave (3) poly spike-wave. Study done at Tanzania suggested 44% of subjects with abnormal EEG having 2.5 Hz generalised spike wave discharges. One of the studies from Sudan involving 32 children showed generalised recurrent discharges.[7]

MRI Brain : In initial stages, MRI can be normal but as disease progresses, atrophy of cerebral & cerebellar area takes place. Superior & middle frontal gyri with prefrontal cortex are markedly affected with relative sparing of occipital cortex & hippocampus. Neuro-pathological examination has suggested that it is one type of neuro-degenerative disorder due to variable degree of tauopathy with no evidence of nematode microfilaria or any foreign organism[7].

CSF Analysis : Most of the cases it's normal with no cells & protein in it[8].

Treatment

Primary treatment of NS is antiepileptic medications and good nutrition. Phenobarbitone, phenytoin, sodium valproate have been tried in different studies. Positive results obtained from one of the largest studies of Uganda with use of sodium valproate where >70% reduction in seizure frequency was achieved. Benefits of dietary supplementation is beyond doubt. Psychiatric counselling, physiotherapy & physical rehabilitation with management of behavioural issues need to be managed effectively which can make the person independent & empower the patient to live their life in better way[9].

In India, although first case of Nodding syndrome was reported from Department of Paediatrics, Vardhaman Medical College & Safdarjang Hospital[10], our case is unique in that it's the first case of Type 1 Diabetes who presented with Nodding syndrome.

Table 2

Stages	Clinical features
First stage	Blankness, generalised weakness, lethargy, starring (develops in 2 years time)
Second Stage	Head nodding
Third Stage	Different kind of seizures including absence seizures & tonic clonic seizures are observed
Fourth Stage	Cognitive dysfunction, motor dysfunction and psychiatric symptoms
Fifth Stage	Severe disability which may end up in parkinsonian features

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Case Report

Struma-ovarii – Literature Review and A Case Report of Malignant Struma-ovarii

Aruna Tantia[1], Sunipa Chatterjee[2], Shashi Khanna[3], Poonam Kapoor[4], Madhu Sudan Banerjee[5], Ushasi Mukherjee[6]

Struma-ovarii are specialized teratomas of thyroid tissue. We report here a case of papillary thyroid carcinoma in struma-ovarii in a morbidly obese woman with review literatures. The ultrasonography revealed a large complex multiloculated right ovarian cyst 10.6x11.1 cm. with solid components. The tumour was removed by laparoscopic salpingo-oophorectomy. On macroscopy, tumour was multiloculated cyst 15x15cm, filled with gelatinous material without papillary excretion and intact capsule. The histological sections demonstrated follicular pattern of papillary thyroid carcinoma's characteristic optically clear nuclei with thickened nuclear membrane, grooving and cellular pleomorphism. The final diagnosis was malignant struma-ovarii, FIGO- Stage-IA. The recovery was uneventful, remaining disease-free for over years. The prognosis is good after conservative surgery Oophorectomy in malignant struma-ovarii when limited to the ovary and the capsule is intact.

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Key words **: Struma-ovarii, Malignant struma-ovarii, Follicular variant of papillary thyroid carcinoma, Teratoma.**

Struma-ovarii is a cystic teratoma of the ovarii[1]. The term Struma-ovarii is assigned to such teratoma of the ovary where thyroid tissue is predominant or its sole consistituent[2].

Gottschalk S were the first to publish a case of true struma-ovarii in late 1890s and considered it arising from ovarian follicles[3]. Gottschalk also noted malignant area in the teratoma and designated it as Folliculoma Malignum. Struma-ovarii occurs at any age between 18-84 years, the peak incidence is in the fifth decade of life, it is more common in left ovary.

There is no biomarker for the Struma-ovarii. Malignancy in struma-ovarii is rare. Lack of universally accepted criteria for malignancy and the varied clinical course contribute to discrepancies in reported cases of malignant struma-ovarii[4].

The actual diagnosis of stuma-ovarii is rarely made until tumour section is examined under microscope. Histopathology of the resected tumour permits diagnosis of struma-ovarii and at the same time confirm or exclude malignancy[1].

Department of Obstetrics & Gynaecology and Minimal Invasive Gynaecology, ILS Hospitals, Kolkata 700064

[1]MS (Obst & Gynae), FMAS, Sr Consultant & Endoscopic Surgeon, Director & Head and Corresponding Author

[2]MS (Obst & Gynae), FMAS, FICMCH, Associate Consultant

[3]MBBS, Associate Consultant Surgeon, Department of Minimal Access and Bariatric Surgery, ILS Hospitals, Kolkata 700064

[4]MBBS, MD (Pathology), Head, Department of Pathology, ILS Hospitals, Kolkata 700064

[5]MD, FRCOG, Ex Professor & Director of IPGME&R, Kolkata 700020

[6]DGO, DNB, Associate Consultant

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Editor's Comment :

- Struma Ovarii are rare specialized teratoma thyroid tissue. They can undergo malignant change 5-10%.
- It does not have definite clinical or imaging characteristics that differentiates it from other ovarian tumours.
- Serum LDH and serum thyroglobulin level may be used to screen it.
- Conservative surgery Salpingo-Oophorectomy can be offered when tumour is limited to one ovary with intact capsule in young patient with good prognosis.

Case Report

A 34-year-old patient presented with complaint of lower abdominal pain for 6 months duration and irregular menstrual bleeding for 4 months. She was morbidly obese with a body mass index (BMI) of 46 kg/m^2. She was on oral contraceptives and had previous abortion and a Lower Uterine Segment Caesarean Section. She was presented with a large abdominopelvic lump of size of 22 weeks pregnancy. Ultrasonography (USG) revealed presence a large complex multiloculated cyst (10.6 x 11.1 cm) in size with septations and solid components (Fig 1-A). Left ovary and the uterus were normal in size.

Triphasic computerized extracorporeal tomography (CECT) (Fig 1-B) confirmed USG findings of multiloculated cyst in the right ovary showing internal density ranging from 33 to 63 HU with solid portion and hemorrhagic fat density, the diagnosis was mature cystic teratoma of right ovary. Cancer Antigen (CA) 125 was within normal range of 6.34 U/mL. The tests of urine, blood, thyroid function, PAP smear from cervix were all normal. Fasting blood sugar was high (155 mg/dl), Serum Lactate Dehydrogenase (502 U/L) & Thyroglobulin level (32.7 ng/Ml.) were normal.

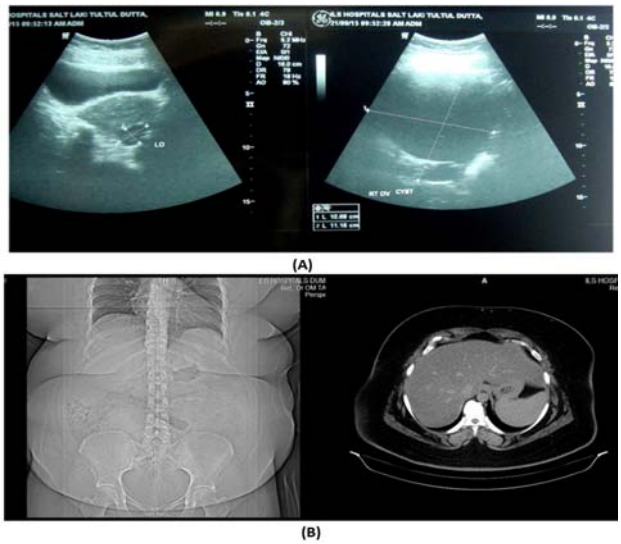

Fig 1 — (A) USG: Large complex multiloculated right ovarian cyst with septations and solid components. (B) – CT scan of lower abdomen: The large multiloculated cystic space occupying lesion (SOL) in the right adnexa showing internal density.

Laparoscopy revealed a large cyst in right ovary, left ovary was normal.

The tumour was removed by Right Salpingo-Oophorectomy by laparoscopic surgery.

On macroscopy, the tumour was a multiloculated cyst 15 x 15 cm. in size filled with gelatinous material (Fig 2-A). There was no papillary excretion or no break in the capsule. The histology demonstrated follicular pattern of papillary thyroid carcinoma characteristic optically clear (ground glass) nuclei with thickened membrane and grooving and cellular pleomorphism (Fig 2-B).

The final diagnosis made was Malignant struma-ovarii, stage – IA, Federation of International of Gynaecologists and Obstetricians (FIGO).

The patient made uneventful recovery and went home on the fourth day of operation. Clinical findings, USG of Neck, CECT Abdomen, Chest X-Ray, Thyroid profile and Thyroglobulin level all were normal at the time of discharge.

Discussion

Thyroid tissue within an ovarian dermoid was first described by Bottlin in 1889 and Pick in 1901 postulated such dermoids as teratomas[4]. Meyer in 1903 first coined the term "Struma-ovarii Colloids". Pick[5] believes that in struma-ovarii the thyroid tissue proliferates while other elements are suppressed in such teratoma.

Histologically struma-ovarii can resemble thryroid adenoma follicular or embryonal type or thyroid carcinoma. Malignancy should be suspected when there is ascites and CA 125 is elevated, Presentation of the struma-ovarii is like that of any other teratoma of ovary and is usually benign. Malignancy in it is reported as 5-10%. Only 21 malignant struma-ovarii with metastasis have so far been reported.

K Zied *et al*[6] reported three cases of struma-ovarii with different presentations.

One a 19 years old girl had menstrual irregularity and a large cystic pelvic mass.

The other was 31 years old, came for investigations of infertility. Routine USG revealed a small cyst in the right ovary and Magnetic Resonance Imaging diagnosed it as teratoma. Third one was 45 years old, parous had intractable menorrhagia and no pelvic mass. She was treated by Hysterectomy with bilateral salpingo-oophorectomy. The right ovary showed, multiple small cysts filled with brown gelatinous material which on microscopy showed evidence of struma-ovarii. Thus struma-ovarii does not have definite clinical or imaging characteritics that differentiates it from other ovarian tumours.

Malignant transformation in Struma-ovarii is extremely low[7]. Hard fixed nodule in the pouch of douglas is not usual neither is ascites. Ascites is not present though the struma-ovarii is malignant because the tumour capsule is not broken down and there is no spread malignant deposits in the general peritoneal cavity. Further ascites could be present in absence of cancerous transformation of the struma where presentation of the case is of pseudo meig's syndrome marked.

Marcus *et al*[8] in their series of seven cases of struma-ovarii described three main histological groups namely: Thyroid tissue predominant in a benign cystic teratoma, the thyroid tissue in cystic adenoma and a pure struma-ovarii.

There is difference in opinion as to what microscopic appearance of the tissue constitute cancer in struma-

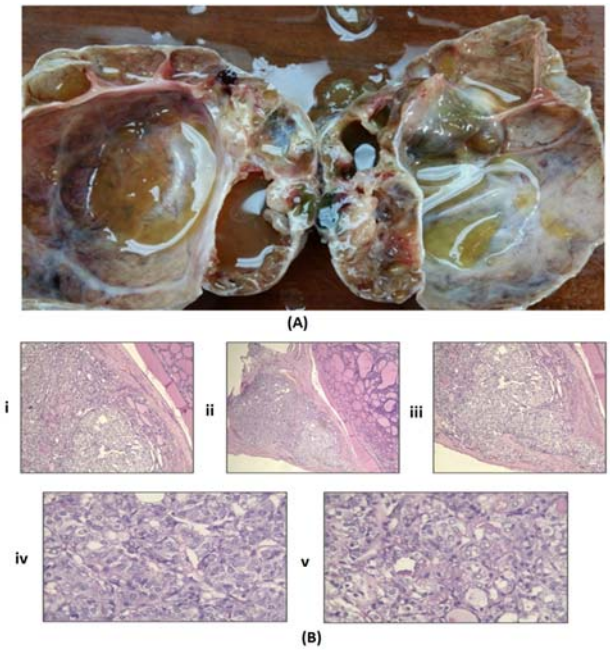

Fig 2 — (A) Cut section of the cyst: showed multiloculated cyst filled with greenish yellow gelatinous material. (B) – Histopathology: Histopathological examination illustrating poorly differentiated thyroid carcinoma arising in struma-ovarii (i) Focal papillary architecture; (ii) Foci of follicular variant of papillary carcinoma in struma-ovarii; (iii) Follicular arrangement; (iv) Nuclei showing grooving; (v) Optically clear nuclei with thickened nuclear membrane.

ovarii. Smith GF[9] held that blood vessel invasion is the only definite criteria of malignancy. Vessel invasion though is difficult.

Vigorous criteria for the diagnosis of malignancy include confirmation of capsular invasion and or metastasis. But evaluation of capsular invasion in struma-ovarii is difficult and can not be used as an essential criteria of malignancy[4].

In general malignancy is diagnosed on the basis of sufficient degree of cellular pleomorphism cytological atypia and mitotic activity. Zakhem *et al*[1] describes two cases of malignancy in struma-ovarii based on histological and nuclear alterations. In his series Devaney[2] describes 14 cases of struma-ovarii using histological criteria of mitosis and ground glass nuclei.

Possibility of metastatic thyroid carcinoma was eliminated in the present case from history, clinical examination, USG of thyroid gland and thyroid functional profile and Thyroglobulin level.

Metastatic struma-ovarii from thyroid carcinoma is rare but from malignancy has to be excluded arising in struma-ovarii. Logani *et al*[10] described a woman who manifested of metastatic papillary thyroid carcinoma in the ovary. The woman was 34 year old and underwent total thyroidectomy for papillary carcinoma of the thyroid gland. Serum thyroglobulin showed significant increase in level from 1.6 ng/ml. to 3.4 ng/ml. in about 3 years period. On follow up of the case, radio imaging with I-131 showed its concentration in the neck and pelvis. Magnetic Resonance Imaging revealed a cystic mass 6 x 4 cm. of size in the left adnexa. The mass removed by Hysterectomy. Histopathology showed it struma-ovarii with features of papillary thyroid carcinoma.

All pathological pattern of malignancy are found in struma-ovarii, but papillary follicular carcinoma is not common. Navarro *et al*[4] in the review of malignant struma-ovarii identified 16 papillary carcinomas, 14 follicular carcinomas and 5 combined papillary carcinoma. To this list they added one of their own case of struma-ovarii which is papillary variant of follicular carcinoma. The case of malignant strum ovarii presented here likewise is the papillary variant follicular carcinoma. Invasion of capsule could not be demonstrated but diagnosis of malignant struma-ovarii is reasonable from the presence of cellular pleo morphism and characteristic nuclear pattern and so may be included in the list of papillary variant of follicular carcinoma in struma-ovarii.

Prognosis of malignant struma-ovarii is difficult to predict because of scarcity of cases and the long intervals before recurrence or metastasis[7]. O'Connel *et al*[11] reported two cases of malignant struma-ovarii. One presented with malignant dissemination to retroperitoneal tissue and lymphglands. Other was of recurrence after ipsilateral Salpingo-Oophorectomy. Re-examination and evaluation of histopathological section of the original mass showed evidence of malignancy.

Salman *et al*[12] reviewed the literature and added one case of papillary thyroid cancer in struma-ovarii. The presentation is similar in the case reported here. In both histology of the mass established the diagnosis and years of follow up showed no evidence of recurrence.

Struma-ovarii is teratoma of the ovary where thyroid tissue predominates malignant variant of it is rare. The presentations are like that of similar ovarian tumours. Histology establishes the diagnosis of struma-ovarii and also the malignant change in it if any.

The prognosis also is good after conservative surgery Oophorectomy in malignancy in struma-ovarii when limited to the ovary and the capsule is intact.

Acknowledgement

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Conflict of Interest : Dr. Aruna Tantia, Dr. Sunipa Chatterjee, Dr. Shashi Khanna, Dr. Poonam Kapoor, Prof. M. S. Banerjee and Dr. Ushasi Mukherjee, declare that they have no conflict of interest and nothing to disclose.

IRB Details : ILS Hospital Ethics Committee Reg. No. – ECR/130/Inst/WB/2013/RR-19 (Validity – 20 April 2019 – 19 April 2024.) has declared on 05.03.2021 that this case report does not need any approval and is exempted for IRB approval.

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Voice of the Expert

Corona Third Wave — Predictions & Preparedness

S Arul Rhaj

Prof (Dr) S Arulrhaj is a renowned physician. He is the Past National President, IMA, Past National President, API & Past Commonwealth President, CMA, UK.
Prof (Dr) Jyotirmoy Pal conducted an online interview on behalf of the JIMA regarding the current COVID Scenario.

An unprecedented upsurge of COVID-19-positive cases and deaths is currently being witnessed across India. According to WHO, India reported an average of 3.9 lakhs of new cases during the first week of May 2021 which equals 47% of new cases reported globally and 276 daily cases per million population. The positive cases and death cases of COVID-19 in India have been highly increasing for the past few weeks, and India is in a midst of a catastrophizing second wave.

On behalf of the journal we would like ask you some questions regarding the CORONA Waves.

We thank you for your valuable time.

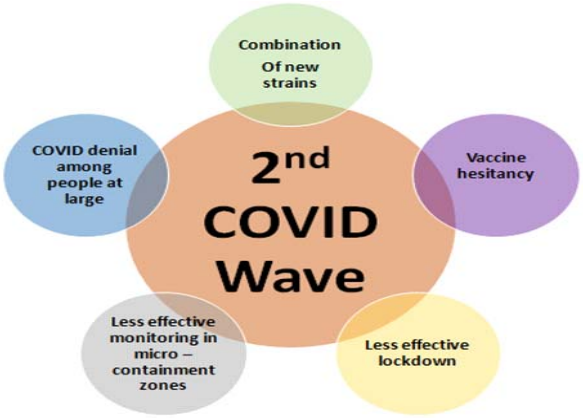
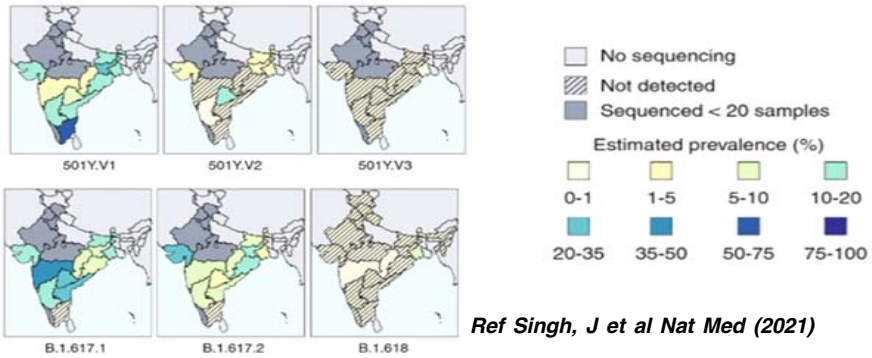


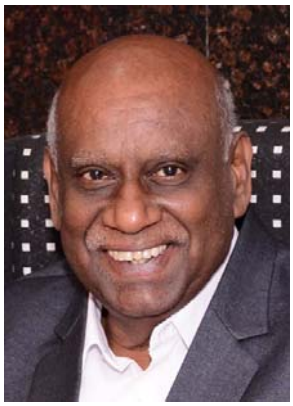
Fig 1 — COVID 2nd wave



Ref Singh, J et al Nat Med (2021)

Fig 2 — Estimated Prevalence of Variants of Concern and Variant of Interest (B.1.618) In Various States of India

(1) What is the meaning of a wave?



Prof (Dr) S Arulrhaj
MD, FRCP (Glasg)

Devoid of a precise technical definition, the term 'wave' is used to signify the rising and falling trends of a disease over a long period of time. The term is also used to describe the seasonality of a disease or infection over successive periods of time.In India there were two distinct waves of Covid-19 infections over the last one year with the first wave reaching its peak in September last year and the second wave beginning from March-April, reaching peak in May. The states of India are interconnected so there are increasing chances of the virus spreading from one person to another person when social distance goes down. This is why states such as Delhi, Karnataka, Tamil Nadu, Kerala, and Maharashtra are mostly affected by the second wave. More penetration was found to Rural India.

(2) What is the 3rd wave?

The third wave currently under discussion refers to a possible surge in cases at the National level. The National curve seems to have entered a declining phase now, after having peaked on May 6. In the last two weeks, the daily case count has dropped. If current trends continue, it is expected that by July, India would reach the same level of case counts as in February. If there is a fresh

surge after that, and continues for a few weeks or months, it would get classified as **the third wave.**

(3) Will the 3rd wave come ?

The Susceptible–Infected–Recovered (SIR) model is formulated for epidemiology. As per SIR Model analysis the third wave will start in the first week of August 2021 and will end during October 2021. As per the result ,**the third wave will take a peak during the first week of September 2021 in India.** Like the second wave, the predicted epidemic rate of the third wave by fractal model shows some peaks after October. **The third wave may be controlled by preventive arrangements, if so then these peaks will not occur.**

Health authorities have been warning of a possible third wave of Covid -19 infections as in other Nations

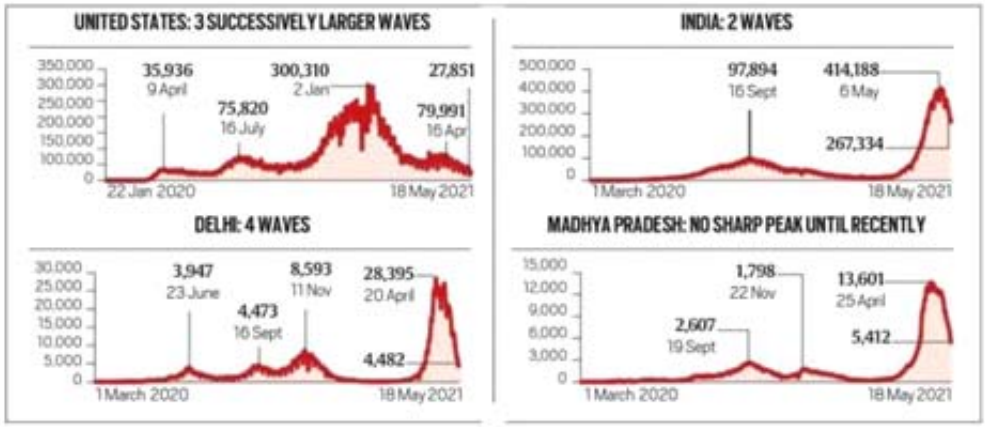


Fig 3

Ref : Clipped from The Indian Express – May 20,2021

(4) Will third wave only affect Children ?

No. Both waves till now saw virus affecting all age groups and mortality was predominantly high in old age people (22%) and the least among children (0.3%). Similar trends in other Nations too.

So clear indication that all age groups were affected in both waves and to large extent in similar way. But as Second wave had 4 times the positivity of first wave it involved much larger population causing bigger havoc. Above Table indicates that age Pattern remained same despite vaccination of older age population.On similar pattern should be the infectivity of Third wave though likely to be on much smaller scale.

Kids usually have mild illness and improve fast. Incidence of serious multi-inflammatory Syndrome **MIS** -C is less than 1: 1000 cases. **Also ACE 2 receptors which provide binding site to Virus for entry into cell are poorly developed in Children making them less vulnerable to COVID-19.**

This data may provide a sigh of relief to all mothers

(5) Is coronavirus 3rd wave inevitable?

The recent emergence of more transmissible COVID-19 variants with higher case fatality poses a serious threat to efforts to control the pandemic. Those variants already identified render anti-viral treatments ineffective, evade immunity from natural infection and, with emerging evidence that some variants reduce efficacy of the first-generation vaccines. It is inevitable that further variants will emerge that pose a more significant threat to vaccine efficacy.

If However, strong measures are taken then the country could altogether avert the third wave.

(6) Will the 3rd wave be more lethal?

Usually as the number of people who have been infected with the disease increases, the successive waves of infection are milder in comparison to the initial waves. However, in case of India, Coronavirus defied this logic as contrary to estimates only a miniscule population of the country had got infected with Coronavirus in the first wave and an overwhelming majority of people were still vulnerable

WHO label	Pango lineage	GISAID clade/variant	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

Fig 4

to Coronavirus. Both **alpha & delta variants** were the main drivers of the second wave in India. New mutants may arise and expected 3rd wave 1.8 time more affection than the second and more severe. Mortality may be reduced.

(7) How to Gear up for third wave?

Govt and hospitals to focus on :

1. Ramping up their ICU beds and facilities especially for children.
2. Improve the infrastructure in the ICU,pediatric and neonatal ICU.
3. Prepare rooms with two portions in room keeping in mind that an attendant will have to be kept with their Covid-positive child.
4. Procuring oxygen masks, high-flow nasal cannulas, pediatric oximeter probes, special ventilators and BIPAP machines &Drugs ,adults& children.
5. Training of health personel for pediatric interventions, neonatologists and paediatric intensivists which could be a serious limiting factor.
6. Installing Oxygen Generators in Hospitals.

Universal Vaccination is the need of the hour

(8) What are the issues about vaccination ?

- To Increase vaccination numbers
- **To Promote vaccination in Rural areas**
- High risk groups to be vaccinated 1st
- After lockdown vaccination to be initiated in big industries , as vaccination camp
- **Vaccine to reach doorsteps .**
- **To Start vaccine between 2 to 18 years soon.**
- **To Make Vaccines effective against Mutants too.** We can expect a more rapid evolution of the virus in 2021 and more new variants as it adapts to humans (biological adaptation) and is now under increasing immunological pressure from infection and vaccination(immunological adaptation).

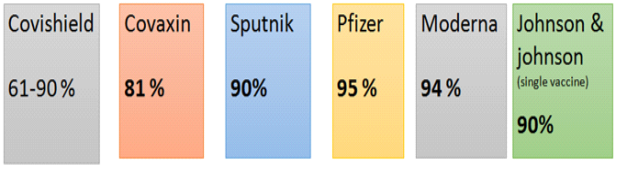


Fig 5 — Efficacy of Vaccines Available Worldwide

(8) What are the ClinicalChallenges in the 3rd wave ?

- **Youth & children**
- **Clinical features**
  Early Breathlessness
  Early cytokinestorm
- **Diagnosis**
  Atypical Presentations
  Mutant Identification
- **Complications**
  systemic inflammation
  Skin & vascular lesions

Covid third wave seems inevitable in late 2021

Mostly caused by Mutants

Sever lung Inflammatory disease will be seen.

Mortality may be reduced.

More Admission Beds& ICU care will be needed.

Will need Boosters with Mutants efficacy

(9) What are the New Normals in 3rd Wave

Treatments

- Doxy Azithro HCQS Ivermectin gone
- Antivirals – Guidelines. Remdesivir gone; New arrivals ?
- Monoclonal Antibodies
- Steroids
- Heparin & Antiplatelets } SUPER HEROES
- Oxygen Administration Nasal catheter, Mask, Rebreathig bag, NIV- CPAP
- Invasive Ventilation– Adult, Paediatric, Neonatal

This being a New Disease the management protocol is likely to undergo many alterations as new evidences trickle in.

(10) What are the responsibilities of the public , Professional Associations, Government ?

- People should reduce hospital visit for simple issues
- **Avoid 3 Cs:** Crowded places, Close contact with others, Confined places with poor ventilation. Wash hands frequently. Wear mask properly

• Parents must not forget their bit to Educate Children and adolescents about Covid Appropriate behaviour, Disease treatment and Self management in Isolation

Professional Associations:

- Sensitise Family Physicians- First Responders.
- Education & Training HCP
- Promote Fever clinics
- Develop Management Protocols.
- Support Government with Bed, care , O2 & Vaccination etc.
- **Public awareness on vaccine**

Government of India

Pandemic Preparedness

UNIVERSAL VACCINATION including Mutants

Invest on Health Infrastructure.

More Testing, Tracking Contacts & Isolation

Travel Checking – Airports.

Vaccination policy for Domestic & International Airports

The numbers, severity, deaths can be diminished or averted with preparedness and preventive measures

(11) What is the Way forward :

- Universal Vaccination
- Preventive Measures continuing-SMS
- More testing, Tracking& Isolation.
- **Target reduction of Infection & Death**

Thank you again Dr Arul Rhaj for your time. We are sure our readers will love to go through this insightful perspective of the COVID waves. We hope to speak with you again in the future.

Pictorial CME

Morphea and Systemic Sclerosis Coexistant : An Uncommon Association

Tathagata Ghosh[1], Kirtiman Mandal[2], Pranabananda Pal[2], Nandini Chatterjee[3]

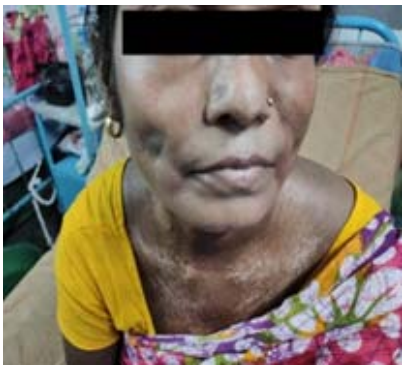


Fig 1 — It shows a depressed scar like lesion at right cheek with hyperpigmentaion of skin over it and salt and pepper like skin pigmentation over the front of chest

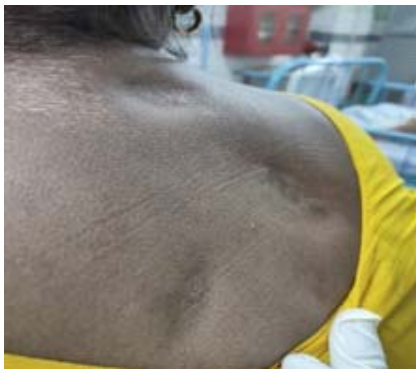


Fig 2 — It shows three discrete depressed scar like lesions at the back of chest with pigmentary changes within two of them

Fig 3 — It shows digital infarcts on left middle finger , ring finger and little finger

A 51 year old female, nondiabetic, hypertensive patient presented with complaints of gradually progressive skin tightening for last 1 year which initially started on fingers and face and gradually involved both upper limbs , neck, upper chest and back along with areas of skin colour changes. She also noted some areas of depressions over right and left cheek and upper back since last 8 months. There was also history of exertional dyspnea for last 6 months. No history suggestive of Raynaud's phenomenon was present.

On examination, patient had pallor, digital pitting scar over fingertips of both hands, salt and pepper like skin over neck, front and back of upper part of chest wall and dorsum both hands. There were 7 sclerotic depressed lesions over both cheeks and back with salt and pepper like changes over some of them. Systemic examination revealed velcro crepitations in both lung fields on chest auscultation and a loud P2 in auscultation of heart.

Investigations showed raised inflammatory markers, Scl70 and ANA positivity, NSIP pattern in HRCT Thorax, moderate PAH in 2D Echocardiography. Diagnosis of Systemic Sclerosis was made in association with Generalized Morphea complicated by Interstitial Lung Disease and Pulmonary Arterial Hypertension. Patient was treated with low dose steroid, PDE 5 inhibitor and planned for monthly injection Cyclophosphamide for 6 months and being followed up.

Morphea, also called as localised scleroderma is a dermatological condition characterized by excessive collagen deposition resulting in thickening of dermis, subcutaneous tissue or may be both. It is caused due to overproduction of collagen mainly type I and III in the affected tissues by fibroblasts probably activated by some immunologic dysregulation. According to clinical features and depth of tissue involvement, Morphea is classified into five subtypes — 1. Circumscribed/Plaque (3 or less discrete lesions) ; 2. Generalized (4 or more discrete lesions); 3. Linear; 4. Mixed and 5. Pansclerotic. Morphea may occur due to infections like Borreliosis, autoimmune causes like scleroderma, radiation therapy, drug induced like bleomycin or D-penicillamine , vaccination like BCG and Tetanus , trauma and chemical exposure. It has a female preponderance. The generalized variant do not have Raynaud's phenomenon or visceral involvement but it is usually linked to a concomitant autoimmune disorder with positive ANA bearing poorer prognosis[1]. Systemic sclerosis is known for its features like Raynaud's phenomenon and widespread visceral involvement. The coexistence of morphea and systemic sclerosis is a very uncommon entity described in 3.2-6.7% cases[2].

This case emphasizes the importance of detailed clinical examination as well as high index of suspicion to detect this type of association between morphea and systemic sclerosis for early intervention and better prognosis.

Department of General Medicine, IPGME&R and SSKM Hospital, Kolkata 700020
[1]MD Student and Corresponding author
[2]MD Student
[3]MD (Gen Medicine), FICP, Professor

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Case Discussion in Obstetrics Gynaecology

Approach to A Case Presented with Bleeding per Vagina

Suparna Biswas[1], Alpana Chetri[2], Subhash Chandra Biswas[3]

Bleeding per vagina as a presenting complaint is found in as high as 1/3rd of females attending health care facilities. In reproductive age groups, it may be due to gestational & non gestational causes. Abnormalities in menstrual cycle involving frequency, regularity, duration & volume of flow is termed as abnormal uterine bleeding (AUB). After excluding pregnancy, the cases are categorized by an acronym for common aetiologies [PALM-COEIN]. Then AUB has to be investigated thoroughly to find out any organic cause, both genital & extra- genital, as per the age group. This article focusses on evaluation and outlines the treatment approach in case of abnormal bleeding per vagina.

[*J Indian Med Assoc* 2021; **119(6):** 73-6]

Key words **: Bleeding per Vagina, Evaluation, Approach.**

Bleeding per vagina as a presenting complaint is found in as high as 1/3rd of females attending health care facilities[1]. In reproductive age groups, it may be due to gestational & non gestational causes. A normal menstrual cycle has a frequency of 24 to 38 days, lasting for 5-7 days with blood loss of 5-79 ml[2]. Abnormalities involving frequency, regularity, duration & volume of flow is termed as abnormal uterine bleeding (AUB), defined by the International Federation of Obstetrics and Gynaecology (FIGO) in 2011. In 2018, they categorized the cases by an acronym for common aetiologies [PALM-COEIN][1]. Globally AUB is reported to occur in 9 to 14% women between menarche and menopause[3]. In India, it is difficult to find the true incidence because the women seek treatment if they are compelled to be absent from work or significantly compromised in quality of life[4]. It may be due to pregnancy related complications or gynaecological (non pregnant) causes.

It is mandatory to rule out pregnancy in woman in reproductive age group presenting with bleeding per vagina by simple urinary pregnancy test unless it is revealed clinically as in late 2nd or 3rd trimester.

In gynaecological cases, the patients are then categorized into different groups viz, prepubertal, adolescent, reproductive age group, perimenopausal & postmenopausal groups. It is better to brush up the possible causes as per the category as follows.

Gynaecology :

(A) Prepubertal : Trauma/sexual abuse/ foreign body in vagina/vulvovaginitis/ precocious puberty/ Exogenous hormones or hormone producing neoplasia (germ cell tumour/ granulosa cell tumour).

(B) Adolescent age group : Anovulatory DUB / Pregnancy related complications/Endocrinology-(Thyroid dysfunction, PCOD)/Coagulation disorders (von Willebrand's disease;ITP)/Infection(PID/genital TB)/ hormone producing neoplasm or exogenous hormones.

(C) Reproductive age group : DUB(ovulatory or anovulatory)/Endocrinopathy (Thyroid disorder, PCOD)/ Neoplasia (eg, leiomyoma, adenomyosis, hormone producing tumours)/Infection (TB,PID)/Exogenous hormone intake.

(D) Perimenopausal age group : Anovulatory DUB/ Neoplasms of upper & lower genital tract (Benign or malignant).

(E) Post-menopausal age group : Endometrial hyperplasia/ cervical or endometrial carcinoma apart from atrophic vaginitis, exogenous Hormone Replacement Therapy (HRT) or pessary.

Editor's Comment :

- Exclude pregnancy first in a woman presented with bleeding P/V.
- Use PALM-COEIN aetiological classification for the diagnosis of AUB.
- Obtain a detailed history and conduct a thorough physical examination to direct the need for further investigation.
- USG is mandatory in any case of bleeding P/V or AUB to evaluate uterus, adnexa and endometrial thickness.
- To offer the best therapy as per aetiology, do proper counselling & follow evidence-based medicine.

Obstetric Causes :

(A) Early trimester-miscarriage/H mole/ectopic pregnancy/implantation bleeding.

(B) Late pregnancy- APH/rupture uterus/ Coincidental cause like piles.

(C) Puerperal/ post abortal complications

With this background knowledge of the possible causes as per age group, a detailed history taking, a thorough clinical examination and relevant investigations are to be done to clinch the diagnosis.

Department of Obstetrics & Gynaecology, IPGME&R, Kolkata 700020

[1]MBBS, MS, First Year Post Graduate Trainee

[2]MBBS, MS (Obst & Gynae), Associate Professor, Department of Obstetrics & Gynaecology, CRSS Medical College & Hospital, Kolkata 700026

[3]MD (PGI, Chd), FICOG, FMAS, FIMSA, Professor

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Diagnostic Approach

A patient with bleeding per vaginally should be approached in the following way:

- Is the patient haemodynamically stable ?
- Is she pregnant ?
- If not what are possible causes of bleeding per-vagina at this age group ?

History

Salient points in history :

Consider the following relevant points during history taking in cases of AUB:

- Age (cause for AUB may vary among different age groups)
- Socioeconomic status (SES; Ca cervix is common in lower SES and Ca endometrium in higher SES)
- Parity (fibroid and endometrial carcinoma are common in nulliparous women; adenomyosis and Ca cervix are commnon in multiparous women)

Presenting complaints Examples of presenting complaints in AUB include:

- H/o excessive bleeding during bleeding phase
- Irregular heavy bleeding
- Continuous bleeding for a few days with preceding amenorrhea for 2-3 months.

Detailed history of the abnormal bleeding should be taken

- Regularity of cycles, duration of flow and amount of bleeding (excessive, average, scanty)
- Pattern of abnormal bleeding-menorrhagia, polymenorrhea, oligomenorrhea, hypomenorrhea, metrorrhagia, and menometrorrhagia
- Associated passage of clots
- Type of protection-sanitary pad/cloth
- How frequently pads are changed (number of pads changed may not correlate with the amount of blood loss)
- H/o preceding amenorrhea (may indicate anovulatory bleeding or pregnancy-related causes.
- Additional symptoms that may provide a clue to the underlying disease are the following:

■ H/o dysmenorrhea- fibroid, adenomyosis, endometriosis, and PID (an ovulatory bleeding usually is not associated with pain)

- Spasmodic dysmenorrhea-in ovulatory cycles
- Congestive dysmenorrhea-in endometriosis and PID

■ H/o dyspareunia-endometriosis

■ H/o infertility-endometriosis

■ H/o abdominal pain-PID

■ H/o vaginal discharge-PID

■ H/o postcoital bleeding (Ca cervix, cervical polyp, cervical erosion, etc)

■ H/o intermenstrual bleeding (submucous fibroid, Ca cervix, cervical polyp, cervical erosion, etc.)

■ H/o combined oral contraceptive (COC) pill or IUCD usage

■ H/o use of any hormones and drugs (unless directly questioned, the patient may not reveal this history)

■ H/o easy bruising/prolonged bleeding from wounds, heavy bleeding after surgery or dental procedures (suggestive of bleeding disorder)

■ H/o fever/cough/night sweats (suggestive of tuberculosis)

■ H/o weight gain, lethargy, hair loss, hoarse voice, cold intolerance, and constipation (suggestive of hypothyroidism)

■ H/o weight gain/acne/hirsutism (suggestive of PCOD)

■ Headache accompanied by visual changes is suggestive of a pituitary tumor.

■ Any thyroid disorder manifested by weight gain, chronic fatigability, alopecia, skin changes to be taken in account

Menstrual History :

- Age at menarche
- Previous Cycles-regular/trregular
- Flow for—days
- Amount of bleeding-excessive, average or scanty
- Associated dysmenorrhea and passage of clots
- Last menstrual period (LMP)

Marital History :

- Married for —— years

■ H/o multiple sexual partners [risk of PID and sexually transmitted diseases (STDs)]

Obstetric History :

- Parity
- H/o of infertility (may be due to anovulation, endometriosis, fibroid, etc, which are causes of AUB)
- Time of last childbirth/miscarriage /mode of termination & any complications thereafter
- Contraception used, if any (irregular intake of COC pills and IUCD usage may present with AUB)

Past History :

- H/o diabetes mellitus (DM) and hypertension.
- H/o surgery
- H/o blood transfusion
- Thyroid disorder
- Tuberculosis

Family history

- Tuberculosis
- Any coagulation disorders
- Family H/o genital malignancy

Physical examination should be directed towards

assessing

- Patient vitals
- Any ongoing bleeding present or nor
- Identifying the aetiology.

General Examination :

- Height, weight, and body mass index (obesity and weight loss are risk factors for ovulatory dysfunction)
- Hirsutism, acne, and acanthosis featiures (PCOD) looked for
- Pallor-to know the severity of bleeding
- Lymphadenopatny (tuberculosis, leukemia or lymphoma)
- Vitals -temperature, puise, BR respiratory rate
- Thyroid examination-any thyroid swelling
- Breast examination- Galactorrhea (prolactinomas is associated with anovulation); any probable mass (fibroadenoma is associated with hyperestrogenism)

Abdominal Examination :

- Palpate for organomegaly-splenomegaly in idiopathic thrombocytopenic purpura (ITP), hepatosplenomegaly in leukemia.
- Abdominopelvic mass may be palpable in structural causes of AUB such as fibroid and adenomyosis

Note *— No mass is palpable in DUB.*

Pelvic Examination

Inspection of external genitalia

Whether healthy or presence of any lesion /ulcers/ growth to be noted.

Per speculum examination

Any cervical and vaginal pathology (cervical growth, cervical polyp, cervicitis, any abnormal discharge, etc) Per speculum and bimanual examination are essential in case presentations (not by under graduate students). Per speculum and bimanual pelvic examination should not be done in adolescent girls who are not sexually active.

Bimanual pelvic examination —

- Uterus size (enlarge in pregnancy, fibroid, adenomysis.)
- Uterine tenderness (present in PID, adenomyosis)
- Adnexal mass (ovarian cyst, ovarian tumour, tubo-ovarian mass, ectopic pregnancy)
- Adnexal tenderness (present in PID, ectopic pregnancy)

Per rectal examination

Nodularity can be felt in POD and along the uterosacral ligament in endometriosis, PID & tuberculosis.

Abdominal examination should be done to assess any lump per abdomen, abdominal tenderness, and peritoneal signs.

Pelvic Examination- Any signs of trauma, foreign bodies, products of conception, presence of bleeding or discharge per vagina.

Per speculum - To assess the source of bleeding, cervical or vaginal trauma, cervical lesions/polyp, cervical discharge etc.

Per vaginal examination- Assessment of uterine size and surface contour, adnexal mass or tenderness, and cervical motion tenderness.

Per rectal examination- To be done in unmarried women, or if the source of bleeding remains unclear, to check for hemorrhoids & any special findings like nodularity.

Laboratory Tests :

- A complete blood count (CBC) is recommended
- Perform a urine for pregnancy test whenever indicated, or if pregnancy is suspected.
- Bleeding time, platelet count, prothrombin time, and partial thromboplastin time are recommended in all adolescents and in adults with a positive screen for coagulopathies. Further testing for von Willebrand disease, ristocetin cofactor activity, factor VIII activity, and von Willebrand factor antigen is recommended in consultation with a hematologist.
- TSH and Prolactin test is done when clinically indicated

Recommendations on Imaging :

- Ultrasonography is mandatory to differentiate Obstetric & Gynaecological cases. In abnormal uterine bleeding, it is to evaluate uterus, adnexa and endometrial thickness.
- Doppler ultrasonography: In suspected arteriovenous malformation, malignancy cases and to differentiate between fibroid and adenomyomas.
- 3D-USG:For evaluating intra myometrial lesion in selected patients for fibroid mapping
- Saline Infusion Sonography (SIS)- To rule out intracavitary lesion such as mucous or fibroid polyp.
- Hysteroscopy: For diagnosing and to know the character of intrauterine abnormalities.
- MRI- To differentiate between fibroids and adenomyomas and mapping exact location of fibroids while planning conservative surgery and prior to therapeutic embolization for fibroids.
- Vaginal cultures or urine polymerase chain reaction (PCR) tests are obtained if infection is a concern.
- Urinalysis with or without urine culture may be needed for women with urinary symptoms

Once Pregnancy Ruled Out :

PALM-COEIN classification for the etiologies of abnormal uterine bleeding proposed by the

Suggested Treatment Options for Abnormal Uterine Bleeding based on PALM-COEIN	
Etiology	**Treatment**
Polyp	Hysteroscopic surgical removal Multiple polyps or polypoidal endometrium and fertility is not desired– LNG-IUS can be combined with surgical removal
Adenomyosis	LNG-IUS, if LNG IUS is not accepted– GnRH agonists with add back therapy; if it fails OCP, NSAIDs, progestogens
Leiomyoma	Intramural or sub-serosal myomas (grade 2-6) Tranexamic acid or COCs or NSAIDs, LNG-IUS, if treatment fails myomectomy depending on location In women >40 years of age, fertility is not desired, for small fibroids (<4- 5 cm)– medical management followed by hysterectomy Short-term management (up to 6 months)– GnRH agonists with add back therapy followed by myomectomy Long-term management– LNG-IUS Newer medical options: ulipristal acetate or low dose mifepristone, currently not available in India Sub mucosal myoma (grade 0-1) hysteroscopic (<4 cm) or abdominal(open or laparoscopic for > 4 cm)
Malignancy	Atypical endometrial hyperplasia– surgical treatment Continued fertility not desired– hysterectomy Hyperplasia without atypia LNG-IUS followed by oral progestins or PRMs
COEIN	LNG-IUS or tranexamic acid, NSAIDs, followed by COCs or cyclic oral progestins Medical or surgical treatment failed or contraindicated: GnRH agonists with add-back hormone therapy When steroidal and other options unsuitable: Centchroman

International Federation of Gynaecology and Obstetrics (FIGO).

To standardize nomenclature of AUB, a new system known by the acronym PLAM-COEIN

(**P**olyp; **A**denomyosis; **L**eiomyoma; **M**alignancy and **H**yperplasia; **C**oagulopathy; **O**vulatory

Disorders; **E**ndometrial factors; **I**atrogenic; and **N**ot classified) was introduced in 2011 by the

International Federation of Gynecology and Obstetrics (FIGO)[5].

The expert committee considered the recommendations of management from the existing guidelines NICE[6,7], supported by SCOG[8] & ACOG[9].

Endometrial histopathology is recommended in women with AUB (Good Clinical Practice Recommendations) :

- All women above 40 years
- In women < 40 years who have high risk factors for carcinoma endometrium such as irregular bleeding, obesity associated with hypertension, PCOS, diabetes, endometrial thickness > 12 mm, family history of malignancy of ovary/breast/endometrium/colon, use of tamoxifen for HRT or breast cancer, late menopause, HNPCC, AUB unresponsive to medical treatment.
- Endometrial aspiration should be the preferred procedure for obtaining endometrial sample for histopathology.
- In case HPE is inadequate or atrophic, hysteroscopy should be performed to rule out polyps.
- Dilatation and curettage should not be the procedure of choice for endometrial assessment.

Obstetric cases are managed by standard treatment protocol as per diagnosis.

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Special Correspondence

[We are publishing this Special Correspondence to commemotare World Thalassaemia Day on 8th May]

Thalassaemia

Sambit Kumar Samanta[1]

The thalassaemia are the commonest monogenic disease in human resulting from quantitative defects of globin moiety of haemoglobin. First described by Cooley and Lee in 1925 as a severe form of anaemia presenting with splenomegaly and bone disease. Whipple, a pathologist coined the term thalassic anaemia, later changed to Thalassaemia from Thalassa or 'the sea', because initially all the patients described, were around the Mediterranean sea. Inherited mostly in recessive manner, the homozygous condition ,the severest form called thalassaemia major, the heterozygous condition termed thalassaemia minor and thalassaemia intermedia which is neither too severe to call it major or not to mild to call it minor. The high frequency of inherited haemoglobin variants in certain regions reflects their heterozygote resistance to Plasmodium falciparum malaria. Heterozygosity for α-thalassaemia, β-thalassaemia and haemoglobin E confer protection against this severe form of malaria. Thalassaemia in its different genetic subtypes mostly prevalent in sub-Saharan Africa, through the Mediterranean region and Middle East, to the Indian subcontinent and east and southeast Asia ie, low-income and middle-income countries bear more than 90% burden of the disease. . Gene drift and founder effects are other reasons that thalassemia are most frequent in these areas. The number of patients with these diseases is expected to increase in the coming years as infant mortality from infectious and nutritional causes declines in many regions of the world.

Magnitude of the Problem :

An estimated 7% of the world population carry an abnormal haemoglobin gene, while about 300,000-500,000 are born annually with significant haemoglobin disorders. They consist of two major groups – Thalassemia and Sickle cell syndromes. Sickle cell syndromes are more frequent and constitute 70% of affected births world-wide, the rest are due to thalassemia. The average prevalence of b thalassemia carriers is 3-4% ie, 35 to 45 million carriers out of 1.21 billion people including around 8% of tribal groups according to the Census of India 2011. India has the largest number of children with Thalassemia major in the world – about 1 to 1.5 lakhs and almost 42 million carriers of β (beta) thalassemia trait. About 10,000 - 15,000 babies with thalassemia major are born every year.

Pathophysiology :

Haemoglobin is a globular molecule made up of four subunits. Each subunit contains a heme, an iron-containing porphyrin derivative, conjugated to a polypeptide, globin. Haemoglobin synthesis is controlled by two multigene clusters on chromosome 16 (encoding the α-like globins) and on chromosome 11 (encoding the β-like globins).The genes are arranged in the order that they are expressed during development to produce different haemoglobin tetramers during embryonic, foetal, and adult life. Within the β-globin gene cluster, the ε-gene is expressed only in early embryos and downstream from this gene are two γ-genes, producing foetal haemoglobin (Hb F,$\alpha_2\gamma_2$)—the haemoglobin form that predominates throughout most of gestation. The δ-gene product forms a minor haemoglobin component, Hb A2 ($\alpha_2\delta_2$), which is useful in the diagnosis of the thalassaemias. The β-gene product combines with α-globin to form Hb A ($\alpha_2\beta_2$), the major haemoglobin component of adult red blood cells. During the first month of gestation, embryonic haemoglobins $\zeta_2\varepsilon_2$, $\alpha_2\varepsilon_2$ and $\zeta\gamma_2$ are formed in erythroid cells located primarily in the yolk sac. During the remainder of fetal life, the sites of erythropoiesis gradually shift from the liver and spleen to the bone marrow, with red blood cells mainly containing Hb F ($\alpha_2\gamma_2$). A switch from foetal Hb to adult Hb expression begins in third trimester and completes by the time the baby reaches 6 months of age. After this time over 95% of the haemoglobin in normal red blood cells is adult Hb A ($\alpha_2\beta_2$) with the remaining haemoglobin consisting of two minor components, Hb A2 and Hb F.

Defects at the molecular level in the α-globin or

[1]MBBS, Associate Professor, Clinical Haematology, Institute of Haematology & Transfusion Medicine (IHTM) and Corresponding author

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β-globin gene clusters form the basis of defective haemoglobin synthesis and the various inherited forms of α-thalassaemias or β-thalassaemias. The type and severity of these clinical forms can also rely on additional and independent intrinsic and extrinsic factors; primary ,secondary and tertiary modifiers. Structural haemoglobin variants like haemoglobin S, C, and E can co-inherit with β thalassaemia thereby producing S/β, C/β and E-β thalassaemias with variable clinical courses.

β-Thalassaemia :

usually present as minor or trait, major and intermedia depending on α-globin or β-globin chain imbalance, severity of anaemia and clinical picture at presentation. Over 300 mutations in the β-globin gene ranging from silent mutations (silent β), to mild mutations that cause a relative reduction in β-globin chain production (β+), to severe mutations with complete absence of β-globin chain synthesis (βo), with deletions of the gene being uncommon.

β-major patients usually presents earlier, approximately 6 months to 2 years of age because á homotetramers in -β thalassemia are more unstable than -β–homotetramers in α-thalassemia and therefore precipitate earlier in the RBC life span, causing marked RBC damage and severe haemolysis associated with ineffective erythropoiesis (IE) and extramedullary haemolysis. Usually major phenotype denotes the homozygous or compound heterozygous forms of the disease, which are characterized by severe anaemia (range, 1-7 g/dL of Hb), haemolysis and massive IE. Presents with severe anaemia characterized by severe pallor, jaundice or growth retardation, accompanied by poor feeding, irritability, decreased activity and/or increased somnolence. Hepatosplenomegaly and In severe thalassemia, IE results in expanded marrow cavities that impinge on normal bone and cause distortion of the cranium, (hair- on- end appearances as seen in skull-x ray) and of facial and long bones. IE, chronic anaemia and hypoxia leads to increased iron absorption from gastrointestinal tract. Transfusion for severe pallor also leads to cumulative iron accumulation (1 unit PRBC contains approximately 225 mg of iron). When serum transferrin saturation exceeds 70%, free iron species, eg, labile plasma iron and pool in RBC increases. These iron species are mainly responsible for generating reactive oxygen species through Fenton's Reaction with eventual tissue damage, organ dysfunction, and death.

β-Thalassaemia minor (trait or carrier) represents the heterozygous inheritance of a β-thalassaemia mutation, with patients often having clinically-asymptomatic-microcytic anaemia requiring no transfusion but genetic counselling. Patients with β-thalassaemia intermedia (TI) can present later in life with mild-to-moderate anaemia and variable transfusion requirements.

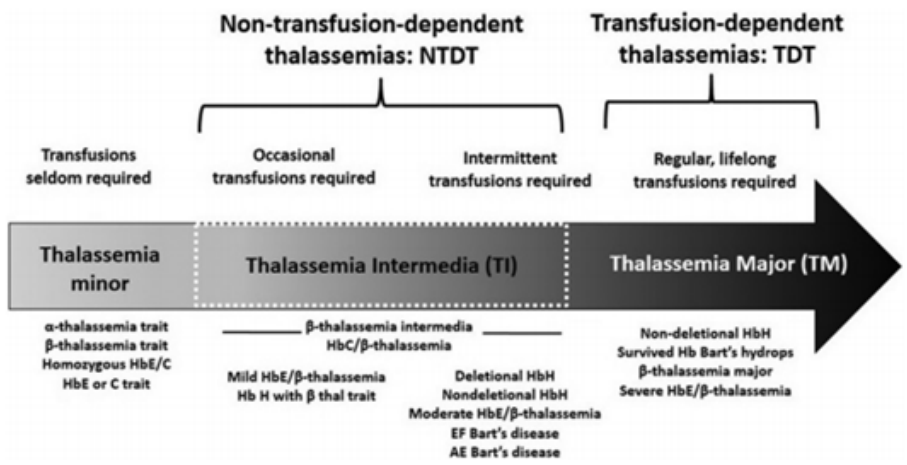
Approximately 10% patients have thalassaemia intermedia phenotypically. Genotypically TI patients may have homozygous or compound heterozygous βo or β+ thalassaemia, homozygous δβ thalassaemia. Concurrent α gene deletion, mutation or triplication or γ mutation may be present with β mutations. Moderate haemolytic anaemia with Hb levels around 7 g/dL without transfusion support is the usual presentation . In TI patients, the clinical phenotypes vary from those with -thalassemia minor to transfusion dependent -thalassemia major (TM). TI patients when require more than 8 units of PRBC annually considered as Major phenotype.

TI patients presents typically at 2-4 years of age, with anaemia, hyperbilirubinemia and hepato-splenomegaly. They have better growth, development, and sexual maturation than TM patients and they typically live longer. The majority of the patients will require episodic transfusions at some point in their lives or when haemolytic or aplastic crises associated with acute infections, folate deficiency, hypersplenism or pregnancy occur. In spite of maintaining Hb more than 7 gm/dl, facial cosmetic defects with depressed nasal bridge and mild malar prominences are usually present. As patients grow older massive splenomegaly with hypersplenism with cytopenia in single or in combination usually occur warranting regular transfusion for improving spleen size and functions and sometimes splenectomy.

In 2012, the new terminology for a clinical classification of thalassemia (TDT and NTDT) was proposed and then adopted by the **Thalassemia International Federation** in their recent guidelines and publications:

α-thalassaemia :

α-Thalassaemia has two main forms, αo-thalassaemia and α+ -thalassaemia and their classifications depend on whether one or both of the linked α-globin genes are deleted or reduced in activity by mutation. The two common forms of α+ -thalassaemia are designated $-\alpha^{3,7}$ and $-\alpha^{4,2}$ to describe the lengths of the underlying deletions. α+ -Thalassaemia result from point mutations, the most common being caused by the chain-termination mutant haemoglobin Constant Spring, designated αCSα. They in heterozygous state are silent and in homozygous state usually present with mild



hypochromic anaemia.

The compound heterozygous states for α+ -thalassaemia and αο -thalassaemia, –α/— or αCSα/—, result in a large excess of β-chain production with the formation of β4 tetramers, known as haemoglobin H. These β4 tetramers are a highly unstable variant of the β-chain and precipitate in RBC causing haemoglobin H disease, characterised by variably severe haemolysis and consequent anaemia. The homozygous state for αο -thalassaemia, —/—, results in the production of tetramers of γ-chains (γ4) known as haemoglobin Bart's. This homozygous state of αο -thalassaemia is associated with a condition called haemoglobin Bart's Hydrops fetalis, which is usually characterised by death in utero or just after birth. Rarer causes of α-thalassaemia include deletions or mutations of regulatory mutations involving the α-globin gene cluster.

Another group of α-thalassaemias that, unlike those described above, occur in no particular ethnic groups: α-thalassaemia and mental retardation; ATR-16 syndrome and ATRX syndrome. Mutation of this ATRX gene sometimes seen predominantly in male patients with mild HbH disease associated with myelodysplastic syndrome.

α-thalassemia usually suspected based on factors, such as a family history of anaemia and geographic and ethnic background where α-thalassemia is common. The diagnosis is suspected in the presence of microcytic hypochromic anaemia not because of iron deficiency, with normal HbA2 levels in Hb electrophoresis. Silent carriers of α-thalassemia and/or α-thalassemia trait are in general clinically asymptomatic and may present with either normal blood count and morphology or with mild microcytic hypochromic anaemia.

Screening and Diagnosis of Thalassemia :

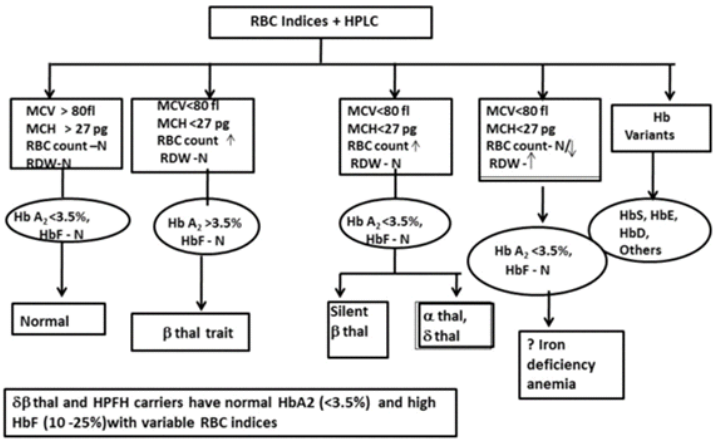
The screening and diagnosis for thalassemia can be divided into 2 levels—population and individual—in which different approaches have been implemented due to different objectives of screening.

Screening Tests for Thalassemia Carriers in a Population Based Approach :

The main purpose of screening for thalassemia carrier status is to identify couples at risk of having offspring with severe thalassemia diseases, such as β-TM, Hb E/β thalassemia, and Hb Bart's hydrops fetalis as the first part of a prevention and control program for thalassemia syndromes.

Diagnosis of Thalassaemia :

(1) Peripheral blood smear : Typical RBC morphology in thalassemia disease shows microcytosis, hypochromia, anisocytosis (variation in cell size) and poikilocytosis (variation in shape). Anisopoikilocytosis results from various abnormal RBC morphology including schistocytes, microspherocytes, target cells, polychromasia, and nucleated RBCs (erythroblasts). nRBC increase proportionately with degree of anaemia and markedly after splenectomy. A



Courtesy : R. Colah et al. / Pediatric Hematology Oncology Journal 2 (2017) 79-84.

characteristic finding is the presence of severe hypochromic, wrinkled and folded cells (leptocytes) containing irregular inclusion bodies of precipitated α-globin chains.

(2) Haemoglobin analysis : Several platforms available for Hb analysis including Hb electrophoresis using cellulose acetate membrane (at pH 8.6), acid agarose (at pH 6.0) or citrate agar gel, isoelectric focusing, low-performance liquid chromatography, high performance liquid chromatography (HPLC) and capillary electrophoresis.

HPLC provides an automated system with a good resolution to discriminate different Hb species. HPLC has been widely adopted worldwide and standard library of Hb variants help making presumptive diagnosis of thalassemia and Hb variants. However, HPLC has a limitation in detecting and quantifying the % of Hb Bart's and Hb H based on their widely used b-thal short program; In addition, it could not separate Hb A2 from Hb E; therefore, these 2 Hb species are eluted into the same retention time and the interpretation of Hb E traits and homozygous Hb E are based on the summation of both Hb E and Hb A2 percentages. Recently introduced a new capillary electrophoresis platform can overcome these problems. Hb E can be separated from Hb A2, and thus can distinguish between homozygous Hb E and Hb E/b-thalassemia.Also detection and quantification for Hb Bart's, Hb H, Hb CS, and Hb Q-Thailand (combined deletion and point mutation on the same allele) for both disease conditions and heterozygotes can be done.

(3) DNA or molecular analysis : These are the most definitive diagnostic modalities. Mutation-specific detection and genome scanning are the two main categories commonly used. Molecular techniques used commonly to detect known mutations, are GAP-PCR using conventional or real-time detection (for gene deletions or insertions), allele-related mutations specific PCR, reverse dot blot hybridization or array-based detection, mismatched-PCR restriction fragment length polymorphism and analyses of a high-resolution melting curve (for point or small nucleotide changes). Although cost effective it cannot detect unknown or rare variations, which might not be included into the panels. Genome scanning (by denaturing gradient gel electrophoresis, denaturing HPLC or single strand conformation polymorphism) and direct sequencing of the whole globin genes would be useful in such situations. Molecular analysis are required only in selective cases but they are very much useful in predicting clinical severity and play important role in thalassaemia control and prevention programme because the mutation data would be required for genetic counseling, genetic risk calculation in the offspring and prenatal and preimplantation genetic diagnosis.

Treatment of Thalassaemia :

Ineffective erythropoiesis, chronic haemolytic anaemia, compensatory hemopoietic expansion, hypercoagulability, and increased intestinal iron absorption are the hallmarks of thalassemias due to the a/b globin chain imbalance and are responsible for several clinical complications.

Thalassaemia Intermedia :

As mentioned previously they are of two clinical types: Non Transfusion Dependent (NTDT) and Transfusion Dependent(TDT). NTDT Patients require episodic transfusions In situations of stress eg, pubertal growth spurt, pregnancy etc. TDT patients are phenotypically like Thalassaemia Major requiring regular transfusions. Although NTDT patients do not get regular transfusions, due to presence of age related chronic anaemia they absorb gastrointestinal iron and iron overload is a recognised complication in them. Serum ferritin to be estimated although above 500µg/L they are not good indicator of iron overload. To overcome this, liver iron concentration (LIC) by liver biopsy(rarely done now-a days due to its invasiveness) or by the more recently applied non-invasive T2* magnetic resonance imaging (MRI) beginning in late childhood or early adolescence should be done.

Extramedullary haematopoiesis, hepatic fibrosis, hypercoagulability, pulmonary hypertension, bone diseases, leg ulcers and cardiac dysfunctions are seen in greater frequencies in comparison to major patients. So these are to be monitored accordingly.

Thalassaemia Major -Treatment Strategies :

Clinical manifestations appear in infancy and include severe anaemia characterized by severe pallor, jaundice or failure to thrive, accompanied by poor feeding, irritability, decreased activity and/or increased somnolence. Hepatosplenomegaly and haemolytic facies. Depending on clinical presentation and laboratory reports decision for initiating transfusion is taken. Poor growth, facial or bone abnormalities and Hb <7 gm/dl are indicator for starting transfusion. Folic acid deficiency and acute febrile illness, blood loss or coinheritance of G-6PD deficiency, need to be addressed before and simultaneously with transfusion therapy. Before first transfusion, patient's RBC should be typed for Rh, ABO antigen and if possible extended panel antibody screening to be done. Parents and First degree relatives should not be donors. Vaccination

against Hepatitis B should be given. For minimising transfusion reactions leucodepleted RBC are preferred, sometimes with bedside leucofilters.

If cardiac failure present then smaller aliquots of RBCs (5 mL/kg) should be administered to prevent volume overload until the Hb level is gradually increased to 9 g/dL. Once a pretransfusion Hb level 9-10 g/dL is achieved, transfusions are administered monthly in infancy and subsequently at 2- to 4-week intervals. In clinically stable patients, 8-15 mL RBCs per kg of body weight can be infused over a span of 1-2 hours at each transfusion event. A record of weight, the amount of blood transfused at each visit and the pretransfusion Hb level is needed to calculate the annual transfusion requirement so that hypersplenism can be diagnosed and decision regarding splenectomy can be taken.

Clinical Complications and Management :

Iron Overload and iron chelation — In TM and TI patients, the rate of transfusional and GI tract iron accumulation is generally 0.3-0.6 mg/kg per day. Ineffective erythropoiesis, haemolysis and severe pallor down-regulate the synthesis of **hepcidin**, a protein that controls iron absorption from the GI tract and increases release of recycled iron from macrophages resulting in increased iron absorption from gut. So Iron overload is an evitable complication in thalassaemia and responsible for many of the clinical complications. Appropriate treatment for combating this iron overload is very important.

3 major classes of iron chelators: hexadentate (deferoxamine [DFO], in which 1 atom of iron is bound to 1 DFO molecule; bidentate (deferiprone, L1 [DFP]), in which1 atom of iron is bound to 3 DFP molecules; and tridentate (deferasirox [DFX], in which 1 atom of iron is bound to 2 DFX molecules presently available.

DFO, with its very short half-life of 8-10 minutes, requires intravenous or subcutaneous parenteral administration. Maintaining normal ascorbic acid levels optimizes DFO iron excretion. The starting dose is 30-40 mg/kg per day for daily use 5-7 days each week in regularly transfused patients. Chelation generally begins between 2 and 4 years of age, after 20-25 RBC units are transfused, with a serum ferritin level 1000 g/dL and an LIC 3 mg Fe/g dry weight. Depending on the efficiency of chelation dose can be gradually escalated to 50 mg/kg and subsequently to 60 mg/kg in adolescents and adults. Before starting and thereafter annually fundal examination and audiometry should be done to avoid ocular and auditory toxicities. **DFP (L1)** is a synthetic compound, absorbed by the GI tract with plasma half-life of 1.5-4 hours. The recommended daily dose is 75 mg/kg per day, which can be increased to 100 mg/kg per day, given orally in 3 divided doses with meals. It removes intracellular iron, and also iron from the heart, improving cardiac function, and preventing iron-induced cardiac disease. The sequential combination of DFP and DFO has an additive chelating effect. The "shuttle hypothesis" suggests that intracellular iron chelated by DFP may be transferred to DFO, a stronger chelator, in the plasma. Subsequently, DFP may renter cells to bind with more iron, inducing greater iron excretion. Agranulocytosis (1%) is a potential risk factor; Weekly blood count monitoring is mandatory for avoiding this.

DFX (Deferasirox), most recently approved (2005) oral iron chelator, highly bioavailable that is absorbed in the GI tract. Because of its relatively long half-life of 12-18 hours, it is prescribed once a day and to be taken in empty stomach. Daily use of a single oral dose of 20-30 mg/kg per day. DFX is also effective in the removal of cardiac iron in hyper transfused rats and TM patients with abnormal MRI T2* cardiac iron. combination of DFX with DFO results in additive iron excretion.

Serum ferritin and creatinine levels and liver function should be monitored closely. Withholding or discontinuation of DFX may be required in cases of unexplained transaminase elevation or progressive increase in serum creatinine or progressive GI symptomatology. In pregnancy who require iron chelation it is recommended to delay chelation until the second trimester and to use subcutaneous DFO. DFX is not approved for use during pregnancy.

Cardiac Complications :

Primary cause of mortality in TDT and to a lesser extent morbidity in patients with NTDT. Cardiac iron deposition occurs mainly in the ventricle, more in the epicardium. Free labile iron interacts with calcium channels and leads to impaired myocardial contractility.

In NTDT, Cardiac iron overload may also affect the conduction system of heart and responsible for conduction delays and heart block. Supraventricular arrythmia particularly atrial fibrillation can be symptomatic requiring prophylactic drug treatment (often with beta-blockers). In uncontrolled or persistent AF, antiarrhythmic therapy and rhythm control with amiodarone and in refractory cases Catheter ablation may be required. Anticoagulation is generally recommended in the presence of AF, heart failure or if the medical history is positive for stroke. Long-term amiodarone therapy may cause hypothyroidism; therapy can often be terminated after 6 to 12 months. MRI T2* is a good tool for arrhythmia prediction.

Cardiac function to be monitored annually beginning at 7 or 8 years of age by ECG, echo, 24-hour Holter monitor and recently by cardiac T2* MRI, which can detect preclinical cardiac iron accumulation. Benign pericarditis, possibly caused by viral and mycoplasmal organisms, bacterial or fungal infections or associated with the engraftment syndrome in post transplantation thalassaemic patients. Pericarditis managed with bed rest and aspirin. Steroids may be helpful with engraftment syndrome and iron chelation with hemosiderosis.

Liver Disease :

Liver is involved in several ways: Transfusion related viral hepatitis with HCV & HBV, secondary haemochromatosis, as a site of extramedullary haematopoiesis and drug induced hepatitis (eg, DFX). In thalassemia patients HBsAg postivity ranges from 0.3% to 5.7% with a higher prevalence of chronic HBV infection in Asia and Southeast Asia countries; Anti HCV antibodies detected in 4.4% to 85.4% of patients In single or concomitant presence of more than one risk factor in a particular patient cause progression of liver fibrosis at an accelerated rate. Chronic liver disease complicated by cirrhosis and ultimately Hepatocellular Carcinoma (HCC), an increasing presentation due to prolonged survival. But assessment of liver fibrosis by noninvasive transient elastography(TE), availability of MRI T2* and good iron chelator as well as effective antiviral drugs and close monitoring can check these hindrances.

Managing Endocrinopathies :

Endocrine complications are very common in thalassaemia patients particularly who are inappropriately iron chelated. The anterior pituitary gland is vulnerable to iron related free radical damage. TDT patients are more prevalent for endocrine complications than NTDT patients. Hypogonadotropic hypogonadism (HH) is the most frequent endocrinopathy encountered ranging from less than 50% to 100%. Iron-induced damage to the hypothalamic pituitary axis can cause delayed pubertal growth and sexual development. Therefore, annual endocrine evaluations are recommended, including measures of pancreatic, thyroid, parathyroid, gonadal function and bone health with nutritional counselling.

Tanner staging should be performed every 6 months in the prepubescent child. For assessment of skeletal maturation annual bone age films and for early detection of growth failure and sexual development monitoring for luteinizing hormone, follicular stimulating hormone, insulin-like growth factor and insulin-like growth factor binding protein-3 from 8-10 years of age should be done. If pubertal changes have not developed by 13 years of age in females, or 16 years of age in males, the use of GnRH and gonadal steroids may be necessary.

Glucose intolerance and Diabetes mellitus can be seen in 20% to 30% of adult patients with β-thalassemia. Starting at 8-10 years of age, annual GTT for the early detection of insulin resistance is recommended to identify prediabetic or diabetic states who may be benefitted from metformin or insulin treatment. For assessment of glycaemic status in these patients fructosamine test is preferred over HbA1C estimation because of alteration of Hb balance.

Bone Disease :

Osteopenia and osteoporosis and increased risk of fractures are almost universal complications of patients with thalassemia, involving both TDT and NTDT, can be more severe in patients with NTDT. Endocrinopathies, iron related toxicities on osteoblasts, chelating agent toxicity (DFO) and Vit D deficiency are some of the contributing factors. Bone Mineral Density (BMD) measured with bone densitometry and calculating Trabecular Bone Score (TBS) by reanalysing spine densitometric images and converting them into a numeric value provides information regarding bone structure. The current treatment of patients with bone disease includes vitamin D and Ca supplementation and bisphosphonates therapy. Recently also denosumab (RANKL inhibitor) and anabolic teriparatide have been introduced for treating osteoporosis in these patients. Also maintenance of optimal Hb level, treatment of concurrent endocrinopathies and promotion of physical activity and smoking cessation are also integral part of the management of bone diseases.

Hypercoagulability :

Thalassaemia patients particularly NTDT and splenectomised ones are prone for hypercoagulability. Low levels of protein C and protein S as well as thrombocytosis and platelet activation, damaged RBC, endothelial injury are contributing factors. Both venous and arterial events, including infrequent thrombotic events in the brain,(5-9%) have been reported. The prevalence of thrombotic events can reach up to 20% in patients with NTDT compared with less than 1% in patients with TDT.

Pulmonary Hypertension(PH) defined as an increase in mean PAP of 25 mm Hg or greater is one of the most significant cardiovascular finding and the main cause of heart failure in NTDT. Endothelial dysfunction, NO depletion following chronic

haemolysis, increased vascular tone, inflammation, hypercoagulability and finally vascular remodelling are underlying pathophysiology. The use of prophylactic antithrombotic therapy for high-risk NTDT patients during surgery, immobilization, and pregnancy, should be considered, as should the use of antiplatelet aggregating agents for patients with thrombocytosis. For PH no prospective RCT in patients affected by NTDT are available for guiding the treatment. Sildenafil citrate, a potent inhibitor of cGMP–specific phosphodiesterase-5, Bosentan, an endothelin receptor antagonist, and epoprostenol, a prostacyclin analogue have shown promising results. However, until now, there are no recommendations regarding if, when or for whom prophylactic antithrombotic treatment is indicated.

Other Complications :

Ineffective erythropoiesis, the hallmark of untreated thalassemia, may cause the expansion of the hematopoietic tissue leading to Extramedullary Haematopoietic (EMH) masses. This is more common in patients with NTDT in whom the reported prevalence is around 20% compared with less than 1% in patients with TDT. Although any body sites may be involved the paraspinal involvement, (11% to 15%) may cause spinal cord compression and paraparesis, which is to be treated on emergency basis Transfusions, hydroxyurea and in some instances, radiation are the management approach to control extramedullary hematopoietic masses.

Cholelithiasis, leg ulcers are among some other complications not infrequently encountered.

Role of Splenectomy :

The therapeutic rationale for splenectomy, particularly in patients with growth retardation and poor health, is to protect against the development of EM haematopoiesis by improving the Hb level, decreasing the transfusion requirement and iron overload. Presently splenectomy done in case of Increased pRBC transfusion requirement > than 200 to 220 mL RBCs/kg per year with a haematocrit of 70%. Hypersplenism ,massive splenomegaly interfering with daily life activities are other indications. Laparoscopic (preferred) or open splenectomy usually done.

Splenectomy should be avoided in less than 5 years of age and should be vaccinated against H influenzae, Pneumococcus, meningococcus as spleen is the site for production of properdin and tuftsin, opsonins responsible for opsonisation of encapsulated bacterias and oral penicillins following splenectomy.

Prevention :

Prenatal diagnosis — Prevention of severe β or α thalassemia births by prenatal diagnosis by CVS (9-12 weeks) or amniocentesis (14-16 weeks) with termination of pregnancies is important way in reducing thalassaemia burden. Acceptance of prenatal diagnosis and termination of affected foetuses are dependent on the early identification of couples at risk, culturally sensitive genetic counselling, the cost, and religious beliefs and it is one of the most difficult ways in addressing the disease.

Cure :

Hematopoietic SCT — allogeneic SCT is the only curative strategy available. Donor selection is of utmost importance; The best results obtained with HLA-matched siblings. Matched unrelated donor or Cord blood are other options. Several risk factors, including hepatomegaly > 2 cm, portal fibrosis and inadequate iron chelation therapy, that can influence the outcome of SCT. Patients are typically classified into 3 risk groups: class 1, those with no risk factors; class 2, those with 1 or 2 risk factors; and class 3, those with all risk factors.

Upcoming Therapies:

Foetal Hb inducing agents- Hydroxyurea, metformin beneficial in reducing transfusion requirement by increasing HbF and total Hb. Foetal globin reactivation by BCL11a inhibitor, Ineffective Erythropoiesis Signalling Modulators (Luspatercept (ACE- 536) and sotatercept (ACE-011) by interfering with signalling molecules in the TGF-β family, such as BMP4, GDF11, and GDF15 showed promising results. Jak2 inhibitor, ruxolitinib and hepcidin mimetics (LJPC-401) are undergoing trial which may in future emerge as promising agents.

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Image in Medicine

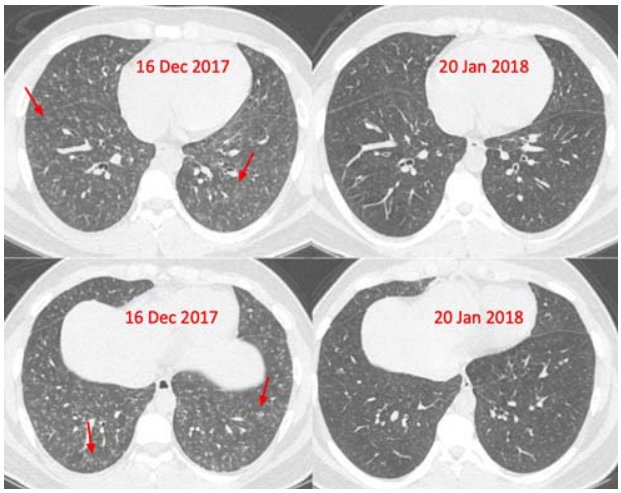
Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

CT scan images of a 23 years old man with 2 weeks history of dyspnea and raised serum IgE levels.

Questions :

(1) What is the most likely diagnosis in this clinical context ?
(2) What are the commonly observed imaging features of TPE ?
(3) What are the other differentials of ill-defined bronchocentric nodules ?



Answers :

(1) Widespread ill-defined bronchocentric nodules are seen diffusely scattered in both the lungs, without any zonal predominance. In view of raised serum IgE levels, these findings are in favour of tropical pulmonary eosinophilia (TPE). Follow up CT scan was done after 3 weeks of diethylcarbamazine (DEC) treatment, which shows significant resolution of the nodules.

(2) Imaging features of TPE are ill-defined bronchocentric nodules, confluent areas of bronchocentric ground glass opacities and smooth interlobular septal thickening. Other findings such as lymphadenopathy, pleural effusions, cavitation and consolidation are also known to occur.

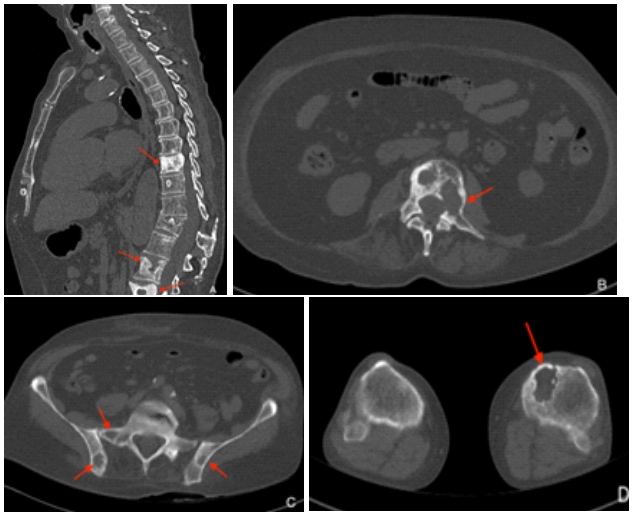
(3) The other differentials of ill-defined broncho-centric nodules are acute inflammatory hypersensitivity pneumonitis, inflammatory bronchiolitis, respiratory bronchiolitis and infectious bronchiolitis.

Quiz 2

A 70 years old man presented with weight loss, loss of appetite and back pain since 4 months.

Questions:

(1) What is the diagnosis ?
(2) What are the common causes of mixed osteolytic-sclerotic metastasis?
(3) What are the common malignancies that spread to appendicular skeleton?



Answers :

(1) Multiple mixed osteolytic and sclerotic lesions are seen involving vertebrae, pelvic bones and tibia. These imaging findings favour diagnosis of metastasis which was confirmed on biopsy. The primary malignancy was carcinoma of prostate, which was also confirmed on Prostate- specific membrane antigen (PSMA) scan.

(2) Mixed osteolytic and sclerotic bone metastasis are commonly seen in malignancy of breast, lung, testis, prostate, cervix and ganglioneuroblastoma.

(3) Metastasis to appendicular skeleton is rare, however it is seen in malignancy of lung, breast, renal and prostate.

Department of Radiology, Picture This by Jankharia, Mumbai, Maharashtra 400004
[1]MD, DNB (Radiology)
[2]MD, DMRD (Radiology)

Student's Corner

Become a Sherlock Holmes in ECG

M Chenniappan[1]

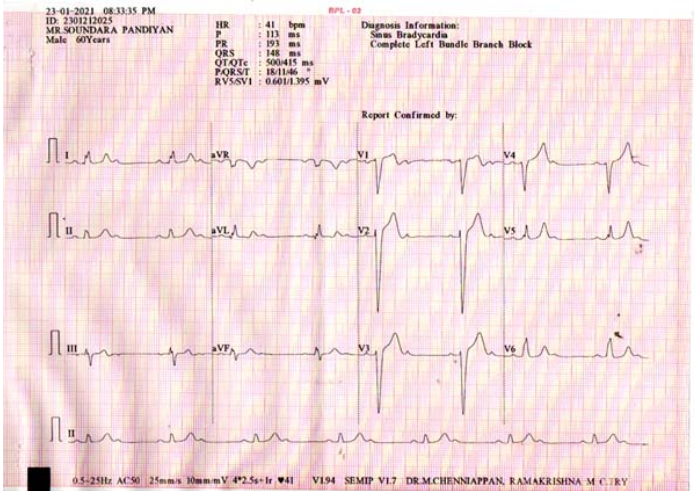
Series 6 :

"Poor man's EPS and CAG"

Routine ECG of 60 years old hypertensive on Amlodipine and Telmisartan.

Questions :

(1) Describe all ECG changes
(2) Why is this clue?
(3) What are practical implications?



ECG Findings:

ECG shows basic bradycardia with complete Left Bundle Branch Block (LBBB). A small wave after each T wave can be an 'u' wave or blocked 'p' wave. The configuration of this wave in V1 as well as the distance of this wave from the T wave are suggestive of 'p' wave. So the blocked 'p' wave can be blocked Atrial Premature Beat (APD) or the sinus 'p ' wave which is blocked. As there is no significant prematurity and change in the configuration of this blocked 'p' wave it is likely to be blocked sinus beat. So, this ECG shows 2:1 AV block. When some 'p' waves are conduced and some 'p' waves are blocked , this is second degree AV Block. However, it cannot come under type 1 or type 2 second degree AV block as there are no two successive PR intervals before the blocked 'p' to decide about whether PR interval is constant or gradually prolonging. This makes 2:1 block as a separate entity of second-degree AV Block. Once second-degree AV block is diagnosed, the site of block is to be determined. For example, in type 1 second degree in AV Block the block is in supra His level (AV node) and in type 2 second degree AV block it is in Infra His level (Bundle branches, fascicles). For 2:1 block , the site of block is decided by PR interval and QRS width. There can be three sites of block (Table 1).

Table 1 — *2:1 AV block - localisation*

Site	PR Interval	QRS
AV Node (Supra HIS level)	Prolonged	Normal
HIS bundle	Normal	Normal
Infra HIS level	Normal	Wide (BBB)

As this ECG shows 2:1 AV Block with wide QRS (LBBB) the site of block is at Infra His Level of bundle branches and or fascicles. Because of LBBB, all the sinus 'p' waves have to be conducted through Right Bundle Branch (RBB) only. But this RBB is conducting only alternate 'p' waves indicating partial disease in itself. Hence, this is Bilateral Bundle Branch Block (BBBB). In addition, LBBB shows homophasic ST T changes (ST and T in the same direction of QRS) in anterolateral and high lateral leads. These signs represent subtle sign of CAD.

The Clue :

As this 2:1 AV block is with wide QRS, the site of block can be diagnosed as infra His AV block from the surface ECG itself without the requirement of electrophysiological studies (EPS). In the presence of LBBB, diagnosis of CAD is difficult as simple tests like exercise ECG may be misleading . So, most often MSCT CAG or regular CAG may be required to diagnose or exclude CAD. The homophasic ST T changes in this ECG in anterolateral and high lateral leads indicate the presence of CAD without more advanced tests as previously mentioned. Because of these reasons the clue of **"Poor man's EPS and CAG"** is given.

Practical Implications :

The presence of advanced AV Block in infra His level manifesting as BBBB will require Permanent Pacemaker Implantation after appropriate evaluation and treatment for CAD.

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

Mediquiz - 06 / 2021

Oxygen Therapy

Chandika Banik, ***MBBS, MD, Anaesthesiology***

(1) All are sources of inhalational oxygen except:
(a) Oxygen cylinder.
(b) Piped medical gas and vacuum (PMGV) or pipelines.
(c) Oxygen concentrator.
(d) Metered dose inhaler.

(2) All of the following statements are true except:
(a) Oxygen saturation is the fraction of oxygenated hemoglobin relative to total hemoglobin (oxygenated + deoxygenated) in blood.
(b) SaO2 is the oxygen saturation of arterial blood determined by arterial blood gas (ABG) analysis. Normal range is 95% to 100%.
(c) SpO2 is the peripheral oxygen saturation level detected by pulse oximetry.
(d) None of the above.

(3) All of the following statements are true except:
(a) PaO2 is the partial pressure of oxygen in arterial blood measured by ABG analysis. Normal range is 75 to 100 mmHg.
(b) Alveolar-arterial oxygen gradient (PAO2 - PaO2) is responsible for diffusion of oxygen across the alveolar membrane.
(c) PaO2 is decreased due to decrease in inhaled oxygen, hypoventilation, diffusion limitation and ventilation – perfusion mismatch.
(d) None of the above.

(4) All of the following statements are true except:
(a) FiO2 or the fraction of inspired oxygen means the concentration of O2 in the inhaled gas mixture which is 21% in room air.
(b) FiO2 is variable with different oxygen delivery devices.
(c) PaO2/FiO2 ratio or P/F ratio is used to determine the severity in ARDS.
(d) None of the above.

(5) All of the following devices can be used to administer 100% FiO2 except :
(a) Simple nasal cannula.
(b) Non rebreathing mask (NRBM).
(c) High flow nasal cannula (HFNC).
(d) Anaesthesia circuit with bag and mask.

(6) All of the following statements are true except:
(a) Hypoxia is defined as reduced level of tissue oxygenation.
(b) Hypoxemia is defined as decrease in partial pressure of oxygen in blood.
(c) Hypoxia and hypoxemia always coexist.
(d) Hypoxemia is a cause of hypoxia.

(7) True statements regarding 'Happy hypoxia ' :
(a) Patients with low level of oxygen saturation (SpO2 <90%) appears clinically well without any significant respiratory distress.
(b) Patients may suddenly deteriorate with acute respiratory failure if this condition remains undiagnosed and untreated.
(c) Happy hypoxia is reported in COVID-19 patients.
(d) All of the above.

(8) All are true except :
(a) Pulse oximetry is a non-invasive method of monitoring peripheral oxygen saturation (SpO2).
(b) Pulse oximeter uses the Beer-Lambert law of light absorption principle.
(c) Inaccurate reading in pulse oximetry occurs due to pigmentation, motion artefacts, hypoperfusion, abnormal hemoglobin etc.
(d) None of the above.

(9) True about oxygen concentrator :
(a) A device that concentrates oxygen from ambient air by selectively removing nitrogen and supplies an oxygen enriched gas stream.
(b) Stationary (home) oxygen concentrators are with higher O2 output (upto 15L/min), lower cost, heavy weight and AC/DC operated.
(c) Portable oxygen concentrators are light weight, with variable O2 flow and output, rechargeable battery operated.
(d) All of the above.

(10) True about oxygen plants :
(a) These are industrial systems designed to generate oxygen from air by using either adsorption technique or membrane separation technique.
(b) The adsorption O2 plants produce 93 to 95% concentration of O2 and used for medical oxygen supply.
(c) The membrane O2 plants produce 30 to 45% concentration of O2 and used for industrial purpose.
(d) All of the above.

(11) Causes of oxygen toxicity are all except :
(a) Hyperbaric oxygen therapy.
(b) Underwater diving.
(c) High concentration of supplemental O2 in premature newborns.
(d) None of the above.

(12) Symptoms of oxygen toxicity are :
(a) Twitching and convulsion.
(b) Difficulty in breathing and chest pain.
(c) Visual disturbances.
(d) All of the above.

(13) True statements regarding ECMO (extra corporeal membrane oxygenation) are :
(a) It is a form of cardiopulmonary life support where blood is circulated outside the body by a mechanical pump, oxygenated with an artificial membrane oxygenator and then reinfused into the circulation.
(b) Respiratory indications of ECMO are severe ARDS not responding to treatment, to provide lung rest in airway obstruction or contusion, post lung transplant.
(c) Cardiac indications are severe cardiac failure due to any cause, post cardiotomy, post heart transplant.
(d) All of the above.

(14) According to ICMR guidelines, severe disease in COVID-19 patients is characterised by
(a) SpO2 <90% on room air or RR>30/min with breathlessness.
(b) SpO2 90 – 93% on room air or RR>24/min with breathlessness.
(c) SpO2 >93% on room air or RR<24/min with no breathlessness.
(d) None of the above.

(15) All of the following measures are useful to improve oxygenation in COVID-19 patients except:
(a) Supine positioning.
(b) High flow nasal cannula (HFNC).
(c) Intermittent positive pressure ventilation (IPPV) with PEEP.
(d) ECMO (extra corporeal membrane oxygenation).

(Answer Page 98)

Special Article

Allopathy (Modern Medicine), Ayurveda and AYUSH : Needs to be In Harmony

H N Dixit[1], Surya Kant[2], Pradeep Dubey[3], Vaidya Madan Gopal Vajpayee[4], Girish Gupta[5]

Healthy life and longevity is the ultimate desire of one and all. There is a difference between disease free life and healthy life. Both of these elements are essential for healthy living. This is high time when about 10 lakhs Doctors of Allopathy (Modern Medicine) and similar Doctors of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) should join hands together to fight against Corona Pandemic and other dreaded diseases like Diabetes, Hypertension, Heart Disease, Liver Disease, Cancer, TB etc. There is no competition or contradiction between Allopathy (Modern Medicine), Ayurveda or other pathies. All are for the good and wellbeing of mankind. There is no justification for cross allegations among them. So-called Propagates of Ayurveda recently criticized and blamed Allopathy (Modern Medicine) for their vested interest. It is against the medical ethics, Indian values and traditions. Such forces which want to create rift between the Allopathy (Modern Medicine) and Ayurveda are against the Society and Humanity. Such people are also weakening the spirit and vision of Prime Minister's Healthy India while all systems of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) are meant primarily for prevention and promotion of health and care of chronic life style related disease, Allopathy (Modern Medicine) is more useful for emergencies, trauma, infections and Intensive care services during the covid pandemic. The services rendered by all pathies were marvelous and fruitful for the management of COVID-19 in India.

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Key words **: Allopathy, Ayurveda, AYUSH, Homeopathy, Harmony.**

Healthy life and longevity is the ultimate desire. There is a difference between disease free life and healthy life. Both these elements are essential for healthy living but herein a conflict between the experts of these two fields has arisen due to vested interest of hand full people. Human body is a complicated structure. The knowledge about the internal functions of human body has been acquired to a large extent. The credit goes to medical scientists. The origin of Ayurveda dates back to about four thousand years before Christ during Rigvedic period and it was developed between 3000-2000 BC. Arthur Anthony Macdonell and Arthur Berriedale Keith have mentioned in the book "Vedic Index" that Indians were curious about the constitution of human body from very early times[1]. Various parts of human body are mentioned in Atharva veda with proper arrangement.

[1]MA, Honorable Speaker, UP Legislative Assembly, Lucknow
[2]MD, Professor & Head, Department of Respiratory Medicine, King George's Medical University, Lucknow 226003 and Corresponding Author
[3]MA, LLB, Principal Secretary, UP Legislative Assembly, Lucknow
[4]BAMS, MD (Panchkarma), Aayush Gram Trust, Poorva Taroha Marg, Surajkund Road, Chitrakoot
[5]MD (Homeopathy), PhD, Chief Consultant, Gaurang Clinic and Centre for Homeopathic Research, Aliganj, Lucknow
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Editor's Comment :

- All the Medical sciences – Allopathy, Ayurveda, and AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy.) should come together joining hands (in harmony) for the medical development and by doing this we will enter into the medical advancement era.
- "We should come together (all sciences) and stand strong"
- In the end, it's all on the patient's will, which science to choose but we can't change that, what we can do is give them the best by joining hands.
- It is the need of the hour to use modern technology, concepts along with all other medical sciences so that they can be applied to offer the best healthcare to society.

These authors have referred to two experts of Ayurveda Charak and Sushrut. HS has mentioned that Indians developed medical science independently[2]. Grammar of Panini includes name of specific diseases[3].

Ayurveda is a unique medical science which emphasizes that one should not become sick. If one becomes sick due to any reason, one should be treated properly. "Its purpose is to protect the health of a healthy person and mitigate the disease of the sick." (prayojanam chaasya swasthsya swasthya rakshanamaataurasya vikaar shamanam ch)[4]. The principles of Ayurveda say that "which medicine produces many other diseases mitigating one disease, is not an appropriate and impeccable way of treatment"

(prayogah shamayed vyadhim yoaanyamanya-mudirayet. Naas au vishuddhah praddhyastu shayed yo n kopayet[5].

Ayurveda is propounded theoretically from Vedas. Knowledge and science is broadly described around the world through teacher-taught traditions. These were named Upanga (second Vedas). "Ayurveda is upanga of Atharv veda"[6]. Ayurveda related thoughts are found in Rigveda also. "Where we found medicines are called "Vedas" and where learned people and rulers protect common people putting their efforts with the use of medicine, are called "vipra"/ "vaidgya/ Dhanvantari." (yatraaushadhih smagyatah rajaanah samitaaviv. Viprah sa uchyete bhishag rakshohaamivachaatan)[7].

In the very first poetic epic Shrimadbalmikiya Ramayana, it is described that in satayuga, Devatas (gods) and Danavas (Demon) had thought to become immortal[8]. For this purpose they organized Samudra Manthana. After a very long period Samudra Manthana, an ayurvedamaya religious fellow appeared which name was Dhanvantari. He forwarded the Ayurveda[9]. It is also found in Shrimadbhagwat Purana also regarding Samudra Manthana and appearance of Dhanvantari who interviewed the Ayurveda[10]. It is also appeared in Mahabharata regarding appearance of Dhanvatari and expansion of Ayurveda[11]. Dhanvantari is also described as profounder of Ayurveda in Agnipurna[12].

In ancient times, there were two schools of Ayurveda – Charaka or Atreya school of Ayurveda, which was basically belonged to physicians basically second was Dhanvantari school of Ayurveda which was belonged to Surgeons. The physicians used to refer patients to surgeons who needed surgery. It is described in Charak Sanhita at many places[13]. It is specially directed in Ayurveda to treat the patient protecting internal fire/immunity of the body. It is so, because of the primary relation of Ayurveda with Rigveda and special relation with Atharv veda and 'Fire' element is appeared from rigveda[14].

Actually the concept of modern medical science started by Hippocrates (Father of modern medicine, born 460 bce, island of Cos, Greece died 375 bce Larrissa, Thessaly) in 4th Century BC. He was an ancient Greek physician who lived during Greece's classic period. It is known that while Hippocrates was alive he was admired as a physician and teacher. The Hippocratic Oath is perhaps the most widely known of the Greek medical texts. It requires a new physician to swear upon a member of healing Gods that he will uphold a number of professional ethical standards. The Hippocratic Oath is one of the oldest binding documents in history. Written in antiquity, its principles are held sacred by doctors to this day: treat the sick to the best of one's ability, preserve patient's privacy[17-19]. Development of Allopathy (Modern Medicine) took place in Europe around 16th and 17th century. Samual Haniman, (Father of Homeopathy) has named it as Allopathy[15].

The science of homoeopathy was invented by a German physician, Dr Christian Friedrich Samuel Hahnemann who was born in Meissen, a small town in Germany on 10th April 1755. He did MD with honours from University of Erlangen in August 1779. The title of his thesis was 'Conspectus adfectuum spasmodicorum aetiologicus et therapeuticus'. (A dissertation on the causes and treatment of spasmodic diseases)[25]. He started clinical practice in 1781 in Mansfeld, Saxony[26,27]. He became dissatisfied with the state of medicine of his time because he observed that patients are coming back with the recurrence of same disease in more aggravated form or modified form. His sense of duty did not allow him to treat the unknown pathological state of suffering brethren with these unknown medicines so he gave up practice and occupied himself solely with chemistry, article writing and translating medical textbooks because he had proficiency in many languages like English, French, Italian, Greek, Latin, Arabic, Syriac and Hebrew[26]. While translating William Cullen's 'A Treatise on the Materia Medica', Dr Hahnemann encountered the claim that cinchona, the bark of a Peruvian tree, was effective in treating malaria because of its astringency. He pondered as to why other astringent substances are not effective against malaria and began to take cinchona himself to study its effect on the human body. He was surprised to note that cinchona induced malaria-like symptoms in him[26,27]. He performed the same experiment on other healthy individuals and got the same result. This led him to postulate a healing principle: "that which can produce a set of symptoms in a healthy individual, can treat a sick individual who is manifesting a similar set of symptoms[26,27]. In 1796, He first published an article about the Homoeopathic approach, in a medical journal of German-language. He later coined the phrase 'Similia Similibus Curantur' which simply means 'Let likes be treated by likes'. It became the basis for an approach to medicine which he gave the name 'Homoeopathy' and first used it in his essay entitled "Indications of the Homoeopathic Employment of Medicines in Ordinary Practice", published in Hufeland's Journal in 1807[28]. In 1810, Dr Hahnemann, the inventor of Homoeopathy, coined the term 'Allopathy'[29] for the traditional European medicine

of the time and a precursor to modern medicine, that did not rely on evidence of effectiveness and sought to treat disease symptoms by correcting the imbalance among the four "humours" (blood, phlegm, yellow bile and black bile) using "harsh and abusive" methods to induce symptoms seen as opposite to those of diseases rather than treating their underlying causes[28,30]. Dr Hahnemann was the one who for the first time demonstrated the therapeutic potential of ultra-high diluted or potentised drugs on healthy as well as sick individuals.

Even though during British colonial period official status of Ayurveda and other traditional healing system were relegated to secondary roles and western medicine became dominant.Calcutta Medical college officially Medical College and Hospital Kolkata is a public medical school in West Bengal. The institute was established on 28th January 1835 by Lord William Bentinck during British Raj as Medical College Bengal. In 1857, the University of Calcutta was found and medical college got affiliated to it. This led to further modernization and modification in curriculum.After independence the Government of India made efforts to recognize Ayurveda, Siddha and Unani[20,21].

Allopathy (Modern Medicine) means a different path. It is called western or modern medical science also. The periphery of its research and system is quite large. It has saved crores of people from fatal illness giving them new life. Surgery, radiation, CT scan and MRI apart from many other medical systems are amazing. During Covid Pandemic lakhs of people were tested. Testing and treatment of this Novel Virus is astounding. Finding of Corona Vaccine in such a short time is extraordinary. Scientists, Doctors and Paramedical staff of modern medicine deserve all praise, who treated Corona infected patients without having regard of their own lives. Till date 1372 Doctors (748 Doctors in first wave and 624 Doctors in second wave) of modern medicine lost their lives in the war against Covid-19 pandemic in India.[22]So contribution of Allopathy (Modern Medicine) has been immense in the COVID-19 Pandemic.

During the time of Pandemic the strength of immunity was discussed all over the country and world. Modern medical science have some supplements as Immunity booster, for this while in Ayurveda healthy lifestyle (Yoga, Pranayam, Meditation, Diet, Biological Clock, Positive thinking and Attitude, Sewa, Sanskar) along with Giloy there are many other medicines for improving the immunity. During the Pandemic the use of medicines like Ashwagandha, Jatamaansi, Guggul increased. Although Ayurveda also had practiced of surgery and Sushruta is considered as Father of Plastic surgery[23].

Isolation became order of the day during Corona Pandemic. In Atharva veda it is said that people should isolate themselves from the society because of decease and they may again come back to normal life[24]. Modern medical science has very good role in emergency, trauma, surgery, Infectious diseases and Intensive Care. Ayurveda and other systems of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) are primarily used for prevention and promotion of health and care of chronic life style related disease, Allopathy (Modern Medicine) is more useful for emergencies, trauma, infections and Intensive care services during the covid pandemic. Ayurveda has medicines to augment immunity. By increasing immunity one can be saved from many diseases. Modern medicine developed vaccines which saved millions of life and Diseases like Small pox and polio eradicated by vaccine only. Acitile and Salicylic Acid are said to be blood thinners. Doctors say that it is a medicine to save from heart attack. Ayurveda also has blood thinning medicines. Side effects is a big problem in the modern medicine. Many Allopathic medicines kill the decease but they also harm the body. Patient needs them for immediate relief. Steroid is a wonderful medicine but has side effects in long term.

Ayurveda is a science of longevity. It includes the health of food, digestion, respiration, deliberation, stress, memory and sleep. Research and Development in Ayurveda were remained neglected in last 1000 years. Ayurveda also requires continuous research, especially in collaboration with Modern Medicine.

There is no competition between Allopathy (Modern Medicine), Ayurveda and other pathies of AYUSH. All the medical sciences are for the good and wellbeing of mankind. All the medical sciences should share its knowledge. There is no use of pointing fingers at each other. Object of both the sciences is the same. Both these sciences have their own qualities and both of them have been developed with scientific outlook. Ayurveda and Allopathy (Modern Medicine) both are sciences but both of them have their own limits. Large part of the world is affected by the diabetes but there is no specific cure for this disease. The treatment of certain diseases may be entrusted to Ayurveda while preliminary treatment of some other diseases may be done by modern science followed by other treatment by Ayurveda. There is a need for continuous dialogue between experts of both the pathies. Confluence of ancient and modern systems is always fruitful for national life in all the fields. Experts of both the sciences

should undertake researches conjointly for medicine and for treatment. There is no justification for cross allegations between them.

So-called Propagates of Ayurveda recently criticized and blamed Allopathy (Modern Medicine) for their vested interest. It is against the medical ethics, Indian values and traditions such forces which want to create rift between the Allopathy (Modern Medicine) and Ayurveda are against the Society and Humanity. This is high time when about 10 lakhs Doctors of Allopathy (Modern Medicine) and similar Doctors of AYUSH should join hands together to fight against Corona Pandemic and other dreaded diseases like Diabetes, Hypertension, Heart Disease, Liver Disease, Cancer, TB, etc. Such people are also weakening the spirit and vision of Prime Minister's Healthy India.[31]

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Drug Corner

Clinical Practice of Prescribing Proton Pump Inhibitors by Physicians : An Indian Perspective

Anish Desai[1], Sunaina S Anand[2]

The proton pump inhibitors (PPIs) are the most widely used category of drugs to reduce gastric acid secretion. The cost of different PPIs vary and could be the deciding factor, especially in India where resources are limited and only a small percent of the population have health insurance. Since no clinical evidence exists to highlight the most effective PPI, the selection of the drug rests with the physician and is usually based on cost and indication. There is need to have systematic assessment of perceptions and practices of health care providers towards the use of this class of drugs. A questionnaire based study was conducted to assess the physician's practice of prescribing PPIs for patients with functional dyspepsia (FD). The aim of the study was to characterize the prescribing patterns so that rationality and cost-effectiveness could be improved in the future. Selection of PPIs depends on indication, lower cost, pharmacokinetics of the drug including rapid onset of maximal acid suppression and less drug-drug interactions.

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Key words **: Proton Pump Inhibitors, Acid Peptic Diseases,**

The proton pump inhibitors (PPIs) are the most widely used category of drugs to reduce gastric acid secretion. There is rising worldwide burden of acid peptic diseases (APDs) due to changing lifestyles and dietary habits. India has a high prevalence of GERD (39.2%), peptic ulcer disease (PUD, 37.1%) and non-ulcer dyspepsia (25.2%)[1]. Available drugs include PPIs, histamine-2 receptor antagonists (H_2RA), antacids, sucralfate and prostaglandin analogues.

The snowballing prevalence continues to increase the global and national demand of acid suppressants. The proton pump inhibitors (only) market in India is estimated to be valued at Rs 2040 Crore (**36.04 Crore units) in 2020** and PPI in combination is valued at Rs 1585.6 Crore (38.25 Crore units)[2]. PPIs are used to treat peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), erosive esophagitis, Zollinger-Ellison syndrome, Barrett's esophagus and upper gastrointestinal bleeding[1]. PPIs have been proven to be superior in the treatment and symptomatic remission of non-erosive reflux disease and erosive esophagitis compared to H_2RAs[2]. They are also used for stress ulcer prophylaxis (SUP) and as gastroprotective agents along with non-steroidal anti-inflammatory drugs (NSAIDs)[3].

The PPIs available in India are Rabeprazole, Pantoprazole, Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Dexrabeprazole and Ilaprazole. There is currently no convincing RCT evidence that one PPI is preferable to another for the management of GERD or PUD related symptoms. The cost of different PPIs vary and could be the deciding factor, especially in India where resources are limited and only a small percent of the population have health insurance[4].

There has been dramatic increase in PPI prescribing patterns over the past several years. There is need to have systematic assessment of perceptions and practices of health care providers towards the use of this class of drug. Even though extensive studies have been investigated on the appropriateness of PPIs in Western countries, such data from India are still very limited. Thus, there is an urgent need to characterize the prescribing patterns so that rationality and cost-effectiveness could be improved in the future. In view of this, we carried out a questionnaire based study to assess the physician's practice of prescribing PPIs for patients with functional dyspepsia (FD). To our knowledge, this is the first study on the use of PPIs among practicing physicians in India.

Material and Methods

Study design: The study was carried out using a self-design questionnaire, developed to assess the clinical practice of prescribing PPIs by general physicians across India. Formal sample size calculation was not carried out, but a target of nearly 400 respondents had been planned. The questionnaire was developed after review of previously published

[1]MD, FCP, PGDHEP, Director, Medical Affairs, Intellimed Healthcare Solutions, Mumbai 400070

[2]Pharm D, Medical Affairs Executive, Intellimed Healthcare Solutions, Mumbai 400070

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studies conducted in other clinical settings.

The first part of the questionnaire consisted of questions regarding social-demographic characteristics of patients with functional dyspepsia such as age, gender and symptoms. The second part involved questions pertaining to choice of PPI in different clinical situations such as chronic kidney disease, surgical cases and geriatric patients. The last part had questions about treatment with PPIs including duration and indication. The physicians ticked the answers based on their clinical practice and observations

Statistical Analysis : Data was entered into Microsoft Excel (MS Office 2007) and statistical analyses were conducted using SPSS 17.0. USA and Microsoft Office Excel 2013. Microsoft India.

Results

Data of all 416 physicians was included in the analysis. The respondents reported that the presence of acid peptic syndrome was majorly found in patients in the age group of 20 - 40 years (58.28%) followed by 40 to 60 years (35.90%). Surprisingly, only 3 respondents reported the presence of APS in elderly people. A slight gender predominance was reported in females (37.76%) than males (34.27%) (Figs 1&2).

Peptic syndrome is characterized by different symptoms such as abdominal pain, growling stomach, nausea, vomiting, burning, acidic taste etc. Physician treating these diseases observed that burning in the stomach or upper abdomen (51.28%) was the most common symptom seen in patients followed by bloating (42.42%), belching and gas (35.43%) (Fig 3).

The questionnaire answered by physicians also included grade of dyspepsia associated reflux in patients during treatment. The respondents reported Grade I reflux frequency to be observed in majority of the patients (32.87%) followed by grade II reflux

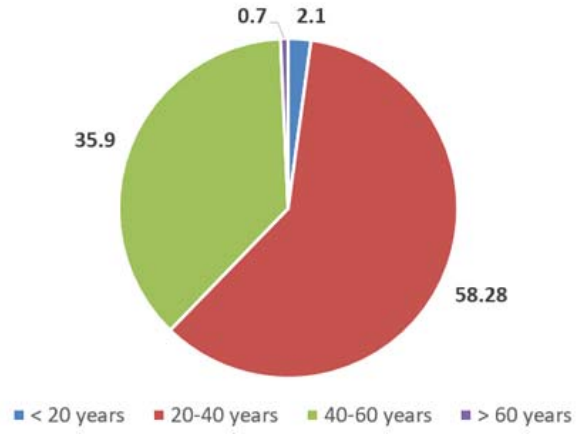

Fig 1 — Age distribution of FD according to respondents

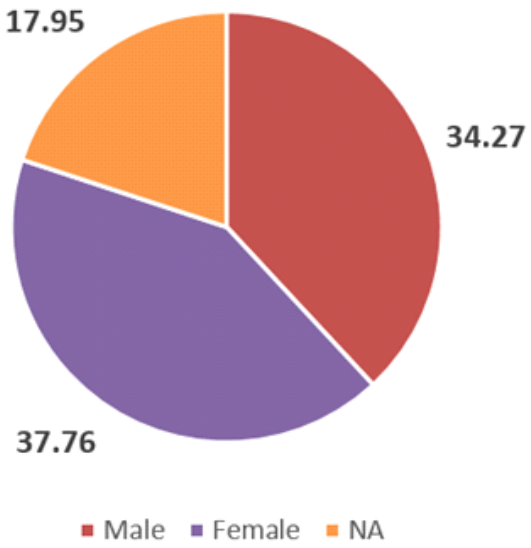

Fig 2 — Gender distribution of FD according to respondents

(28.44%). Respondents reported higher frequency of grade III ulcers than grade II (27.51% *versus* 20.05%). Similarly according to the physicians, grade II and grade III dysmotility was much more observed in patients (Table 1).

The use of PPI in patient is determined by different associated disease conditions & age of the patient. Patients of CKD often complain about dyspeptic symptoms due to increased production of gastrin. The physicians reported maximum use of Rabeprazole (32.63%) followed by Pantoprazole (25.41%) in patients with chronic kidney disease (CKD). If the patient underwent surgery, most physicians preferred pantoprazole (22.61%) & combination of pantoprazole + Domeperidone (26.81%).In geriatric patients, the respondents preferred combination of Domperidone and Pantoprazole followed by the combination of Rabeprazole and domperidone (Table 2).

Furthermore, the most common choice for GERD treatment by the respondents is combination of Rabeprazole & Domperidone (21.45%) as it has high symptom improvement rate. During answering questionnaire, physician answered the regular use of proton pump inhibitors (PPI) in the treatment of dyspepsia & found that Pantoprazole (13.29%) & combination of pantoprazole with Domperidone (28.44%) was preferred over other PPIs.Also, majority of physicians (38%) recommended use of PPI for the duration of 3-5 weeks in dyspepsia treatment (Fig 4 & Table 3).

Discussion

Increasing urbanization and poor eating habits has

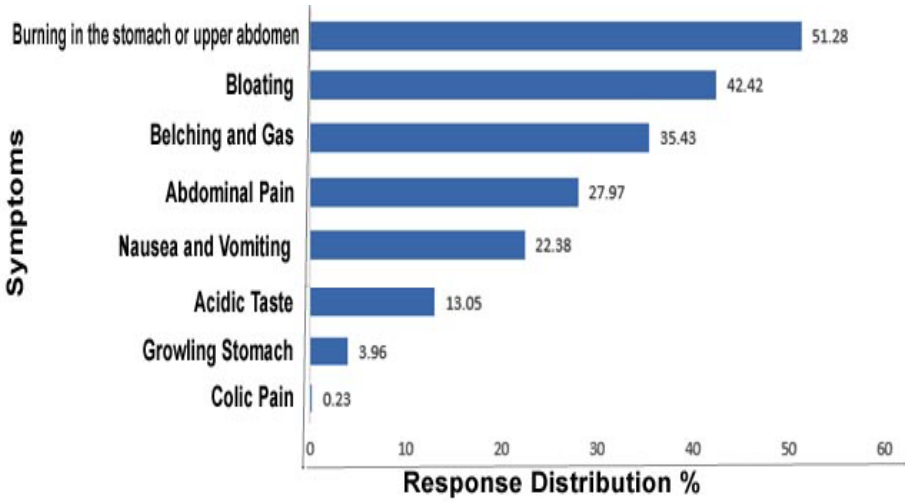

Fig 3 — Symptoms of FD according to respondents

Table 1 — *Grade of reflux and dysmotility in FD according to respondents*

	Response distribution %	
	Reflux	Dysmotility
Grade 1	32.87	15.38
Grade 2	28.44	24.48
Grade 3	16.55	24.71
Grade 4	8.16	11.19
Grade 5	6.29	6.06

Table 2 — *Choice of PPI based on clinical situation of the patient*

	Response distribution %				
Choice of PPI	CKD	Surgery	Geriatric	GERD	Dyspepsia
Acotiamide	2.33	0.23	0.47	1.40	1.86
Esomeprazole	15.15	10.96	17.02	12.59	11.19
LANSOPRAZOLE	0.23	0	0.23	0	0
Omeprazole	9.56	2.80	7.69	5.59	6.76
Pantoprazole	25.41	22.61	18.65	11.42	13.29
Pantoprazole+ Domperidone	12.59	26.81	13.29	31.47	21.91
Pantoprazole+ Levosulpiride	6.29	5.59	6.06	8.16	6.29
Rabeprazole	32.63	21.21	29.60	17.48	23.78
Rabeprazole+ Domperidone	20.75	23.08	22.61	21.45	28.44
Rabeprazole+ Levosulpiride	6.29	7.46	6.29	20.05	12.82

accentuated the global burden of acid peptic syndrome. Physicians often face the difficulty of choosing the PPI since there is no concluding evidence to highlight the most effective PPI for the management of PUD or GERD or for endoscopically confirmed healing of esophagitis[4]. Thus, physicians base their selection of PPI on cost and indication. Thus treatment varies based on both patient and physician. Due to lack of standard guidelines a huge variation exist in selection of PPIs. Our study was conceived in this context to capture data regarding the clinical practice of prescribing PPIs by general physicians in India. As far as clinical practice is concerned, this study is the first one of its kind in India.

Guidelines from the National Institute of Clinical Excellence (NICE) does not differentiate between PPIs except on the grounds of cost and accepted indications. Furthermore, a review of the pharmaco-logical properties of the four standard PPIs omeprazole, Lansoprazole, pantoprazole and Rabeprazole also concludes that they are essentially similar in efficacy[5,6]. Hence, unless one drug is shown to be clinically superior, it seems reasonable to choose the PPI based on cost.

Coming to pharmacological action, Lansoprazole and Rabeprazole have a more rapid onset of maximal acid suppression than the other PPIs. Both Pantoprazole and Rabeprazole, there is a linear relationship between dose and plasma drug concentrations after single and multiple dose administration and there is no reduction in bioavailability of Pantoprazole if concurrently administered with antacids. Rabeprazole has less potential for drug interactions and no interactions of clinical relevance have been reported for Pantoprazole. PPIs share a common mechanism of action but pantoprazole and Rabeprazole show greater selectivity for the cysteine 813/822 sites of the proton pump. Rabeprazole converts rapidly to the activated sulphenamide form and dissociates more readily from the H^+K^+ ATPase than the other drugs, exhibiting a faster rate of inhibition and shorter duration of action[6].

Data was gathered from 416 general physicians was included in the analysis. The respondents reported that the presence of acid peptic syndrome was majorly found in patients in the age group of 20 - 40 years and is similar to a study conducted in Asian patients. Though such an age distribution is seen, many studies suggest that age and ethnicity are not predictive factors for FD[1]. The prevalence of peptic ulcer disease has

Table 3 — *Preference of PPIs among respondents based on indication and clinical characteristics*

	Choice of PPI according to respondents		
	First choice	Second choice	Third choice
CKD	Rabeprazole	Pantoprazole	Rabeprazole +Domperidone
Surgery	Pantoprazole +Domperidone	Rabeprazole +Domperidone	Pantoprazole
Geriatric	Rabeprazole	Rabeprazole +Domperidone	Pantoprazole
GERD	Pantoprazole +Domperidone	Rabeprazole +Domperidone	Rabeprazole + Levosulpiride
Dyspepsia	Rabeprazole +Domperidone	Rabeprazole	Rabeprazole + Levosulpiride

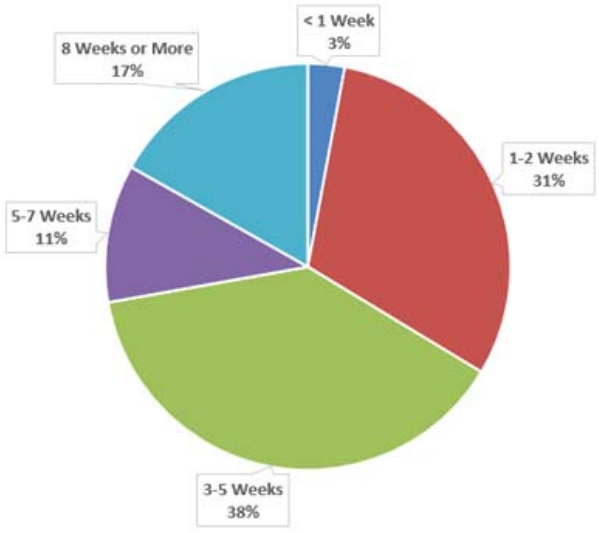

Fig 4 — Duration of PPI in dyspepsia treatment

shifted from predominance in males to similar occurrences in males and females. Our study too reported similar occurrence in men and women. The lifetime prevalence is approximately 11%-14% in men and 8-11% in women[7].

Rabeprazole was the PPI of choice by the respondents followed by Pantoprazole (25.41%) in patients with chronic kidney disease (CKD). The reason could be that no dosage adjustment of Rabeprazole is required in patients with renal dysfunction. Deprescribing PPIs is important when there is no clear indication for use[9]. There is a strong and consistent association between PPI use and increased risk for incident CKD, CKD progression and kidney failure. Hence, careful monitoring of renal function and cessation of PPI is very important in such patients to reduce the population burden of CKD[10].

If the patient underwent surgery, most respondents preferred pantoprazole alone or in combination with Domeperidone. This may be based on the reason that Pantoprazole has the least drug interactions and patients in the surgical department are generally on many medications. To avoid potential drug-drug interactions, physicians may prefer Pantoprazole as the PPI to prevent stress ulcers. PPIs are used for stress ulcer prophylaxis in critically ill patients including surgical ICU patients[11,12]. Furthermore, most PPIs are uniformly effective for reducing gastrointestinal bleeding in ICU patients receiving mechanical ventilation[13].

Elderly patients are particularly likely to be prescribed acid suppression drugs. In geriatric patients, the respondents preferred combination of Domeperidone and Pantoprazole followed by the combination of Rabeprazole and Domeperidone. PPIs should be used at the lowest dose and for the shortest duration possible in geriatric population. They are still relatively safe drugs but should only be prescribed for proven indications[14]. Pantoprazole shows to have minimal interactions with other drugs because of its low affinity for cytochrome P450 than older PPIs. Although, majority of elderly patients have comorbidities and receive other drugs, the efficacy of Pantoprazole may not be adversely affected, attributable to its Pharmacokinetics, which are independent of patient age. Clinical practice suggests that a low dose maintenance of PPIs should be used in older patients with GERD[15].

Furthermore, the most common choice for GERD treatment by the respondents is combination of Pantoprazole & Domeperidone. During answering questionnaire, physician answered the regular use of proton pump inhibitors (PPI) in the treatment of dyspepsia & found that Pantoprazole (13.29%) & combination of Pantoprazole with Domeperidone (28.44%) was preferred over other drugs. No solid evidence is available to point out the most effective PPI for GERD, thus selection depends on cost and indication[16]. In India, the prevalence of GERD ranges between 7.6 - 30%[17].

Most of the physician recommended use of PPI for the duration of 3 to five week in dyspepsia treatment. Authors of a Cochrane review concluded the duration of the PPI treatment for functional dyspepsia (FD) is at least two weeks[18]. There is no standard for duration since it depends on the patient's improvement, cost and indication. An expert review provided key recommendations for decision making in order to

minimize the irrational use of PPIs. Those patients with GERD and acid-related complications must take a PPI for at least 12 weeks for healing of esophagitis, and for maximum up to 48 weeks for symptom control. Patients with Barrett's esophagus should take long-term PPI. Those patients at high risk for ulcer-related bleeding from NSAIDs must take a PPI if they continue to take NSAIDs[1]. These recommendations would assist the physicians in taking treatment related decisions.

Drug-induced gastrointestinal (GI) symptoms with NSAIDs, metformin, antibiotics and anti hypertensives are commonly encountered in clinical practice.Given the common use of these drugs in clinical practice and the rising burden of chronic diseases including cardiovascular disease and diabetes, it is not at all recommended to discontinue these drugs. Furthermore, failure to recognize and prevent drug-related symptoms may lead to unnecessary investigations and treatment. It seems reasonable that co-prescription of a PPI be considered when there is a risk of drug-induced gastritis[19].

Gastric mucosal injury and adverse reaction caused by NSAIDs is clinically problematic. About 25% of patients using NSAIDs develop peptic ulcer. In one study, treatment efficacy (endoscopic cure rate) of Rabeprazole for NSAID-induced ulcer under continuous NSAID administration was 71.1%[20]. In another study it was seen that PPIs significantly reduced gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors[21]. Low-dose Aspirin (LDA) also reduced cardiovascular events by about 25% in comparison to non-use but increase gastrointestinal events two- to five-fold. The use of long-term Rabeprazole 10-mg and 5-mg once daily prevented the recurrence of peptic ulcers in subjects on low-dose aspirin therapy, and both were well-tolerated[22]. Thus, these two studies confirm that the proton pump inhibitor (PPI),Rabeprazole is highly effective in preventing upper GI ulcers or bleeding in patients taking low-dose aspirin or NSAIDs.

The 2017 joint American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) guidelines recommended standard-dose PPIs as first-line treatment in patients with H. pylori–negative functional dyspepsia. Those patients with H pylori–positive dyspepsia, must take PPI if eradication is unsuccessful at reducing symptoms. The guidelines also pointed out that low dose therapy is as effective as standard-dose therapy[18].

Despite the useful information learnt from this study, several limitations require mention. First, our findings about clinical practice of prescribing PPI for functional dyspepsia among physicians are based on a self-reported instrument. Secondly, the small number of respondents cannot account for all the physicians in the country.

Conclusion

Our study is one of its kind to gather data on clinical practice of prescribing PPIs among physicians in India. The snowballing rise of acid peptic diseases have given rise to a variety of PPIs. Since no clinical evidence exists to highlight the most effective PPI, the selection of the drug rests with the physician and is usually based on cost and indication. The data from our study indicates that the majority of the respondents prefer Rabeprazole and Pantoprazole for functional dyspepsia in most clinical situations including surgery, CKD and elderly. Rapid onset of maximal acid suppression, drug-plasma linear relationship, less drug-drug interactions and low cost may be attributable factors. PPIs have a huge economic burden on the patient as well as the country. Hence, understanding the prescribing preference of PPIs is important in developing countries, such as India, to improve rationality and cost-effectiveness of PPIs.

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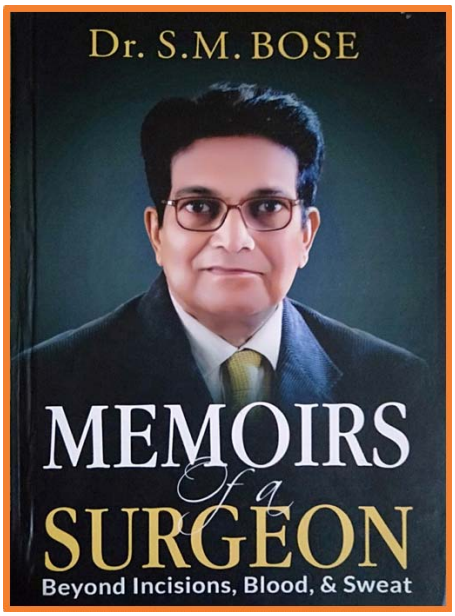
Book Review

"Memoirs of a Surgeon Beyond Incisions, Blood, & Sweat" by Prof Shashanka Mohan Bose, July 2020, Published by Dr Shashanka Mohan Bose, H No 215, Sector 36, Chandigarh 160036, 22 Cm x 15 Cm, Rs 600.00. US$ 15.00.



I had shared over three decades with Dr Bose while serving on the Faculty of the PGIMER, although in a non-surgical department. Our paths crossed almost every day in our day to day life at the Institute both during and off the working hours. He was an overwhelming and multifarious personality who was there in almost all areas of the Institute. It is no surprise that he has come out with this book with glimpses of different aspects of life and character of the institute almost as much as of his journey.

The autobiography by Dr S.M. Bose is a welcome publication worth reading by doctors and the lay alike. It gives an insight into the life and work of a doctor, particularly a surgeon about the struggles faced every day. He cherishes his success after a challenge is over but waits for the new one to come even before the first is over. As has been aptly name as '...beyond incision, blood and sweat', the book provides interesting glances into scenes behind the curtains. People know a surgeon as a person who cuts, bleeds and sutures. That is only the tip of the iceberg. The surgery is the visible tip. Dr Bose describes the qualities of a surgeon in a pictorial manner as the man who has the '*eyes of an owl, hands of a lady, heart of a lion, smelling power of a dog and stamina of a donkey'*.

Superficially, the book looks like a simple life-history of a doctor who has his or her own stories of ups and downs. But Dr Bose has much more to tell in a simple and sequential manner. He talks about his talented wife and daughters, friends, colleagues and teachers. It is remarkable to learn how he could do justice to both his profession and his family. Neither of the two was disappointed with him but for an occasional incident. He continued to rise higher and higher and achieved several heights which many others would envy.

Dr Bose cites interesting anecdotes about his professional work both in India and abroad. While in Libya, he was greatly admired as '*Hindi Jarrah'* (Indian Surgeon) and performed the work of a surgeon, a gynaecologist, a neurosurgeon , an Orthopaedic Surgeon , an Administrator and so on. He also undertook surgery for infants and children with as much ease as for adults. During his later career, he restricted himself more to adults and made his name as a specialist surgeon with particular interest in breast cancer. Factually, his whole professional life proved his skills with his knife and personality alike. Many surgeons with great skill, influence and riches are not easily available for disinherited patients but here is an outstanding life well spent in the service of a common man, training young surgeons to serve the society in the true traditions of profession.

He was good in studies and took active part in cultural and social activities. He was also good in sports - football, kabaddi, hockey, Table Tennis. He was admired because of leadership qualities; he chaired many organisations, right from his college days to professional peak time Such multifaceted activities are rare in one individual. I am sure that readers will enjoy the book especially about his memoirs and anecdotes. I wish the very best for Dr Bose ever in his life.

Former HOD, **Prof S K Jindal**
Pulmonary Medicine,
PGIMER, Chandigarh

* * * * *

It has always been a pleasure interacting with Professor Bose, a multifaceted personality, a powerhouse of energy, an able surgeon, conniver of art and now an author of repute. It was indeed a privilege to receive a copy of his memoirs. It is so engrossing that it reads like a novel with a perfect blend of snippets, travel experiences in different countries ,very precious photographic memories with stalwarts in medicine and in other fields, fascinating reminiscences by students and teachers , innovations in surgical skills and "salt and pepper episodes " adding a touch of fiction.

It indicates that a lot of home work has been done to publish this book and Professor Bose has set a very high benchmark for memoirs and those planning to write memoirs, must read this book.The book also unfolds his panoramic personality as an artist, nature lover, photographer , a surgeon of repute with great organizational skills and a master story teller.

The book has an excellent quality of paper and print, the text has been arranged flawlessly with appropriately spaced words of wisdom.

In all, It makes a perfect reading both for doctors and non doctors alike . I would like to congratulate Professor Bose for this great endeavor and I would strongly recommend this book to one and all.

Former HOD **Prof Shobha Sehgal**
Immunopathology & Professor Emeritus,
PGIMER, Chandigarh

Letter to the Editor

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

End TB by 2025 : Tribal Perspective

Sir, — We read with interest the article on 'End TB by 2025: Way forward to achieve this mission while recovering from the COVID-19 Pandemic' by Dr Surya Kant in your April 2021 issue. Dr. Surya Kant has discussed in detail the TB situation in the country and the possible impact of Covid 19 on tuberculosis burden in the country. The article also mentions about the commitment of Government of India to eliminate TB by 2025 – five years ahead of the Global target. The NTEP has developed the National Strategic Plan (NSP) 2017-2025 to achieve the targets set to achieve the goal. While the country is taking steps to achieve the goal, the tuberculosis situation in vulnerable population groups deserves special attention. The tribal population is one of these vulnerable groups in the country. According to Census of India -2011, the Scheduled Tribe population in the country is 104 million constituting 8.6% of the country's population. Though, the information on TB situation in tribal population is limited, the available literature point towards high TB burden especially in some tribal groups such as Saharia – a Particularly Vulnerable Tribal Group (PVTG) in Madhya Pradesh. A series of studies conducted by our group reported a very high TB prevalence ranging from 1518 to 3294/100000 population among them which is five to ten times higher than the national average. The disproportionate disease burden remains a huge challenge for India's TB elimination programme especially in view of our goal of 'Ending TB by 2025'. Though the decline in TB prevalence in this tribe has been reported, there is no room for complacency as it is still alarmingly high and is a matter of concern. What is more worrisome at the present time due to COVID-19 is the overburdening of already inaccessible health services in most tribal areas. This may further deteriorate the TB situation in high TB burden tribal communities. Considering these and to bring TB elimination in to reality, there is an urgent need to frame realistic action plan to address high TB burden in tribal groups such as Saharias in Madhya Pradesh.

National Institute of Research in in Tribal Health, Jabalpur 482003
*Corresponding author

V G Rao*,
Jyothi Bhat,
Rajiv Yadav

(Answer : Mediquiz 06/2021)

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For Reception	**:**	**Mobile : +919477493033**
For Editorial	**:**	**jima1930@rediffmail.com**
		Mobile : +919477493027
For Circulation	**:**	**jimacir@gmail.com**
		Mobile : +919477493037
For Marketing	**:**	**jimamkt@gmail.com**
		Mobile : +919477493036
For Accounts	**:**	**journalaccts@gmail.com**
		Mobile : +919432211112
For Guideline	**:**	**https://onlinejima.com**

Indian Medical Association HQ

MUCORMYCOSIS

Guidelines for the Diagnosis & Management

Dr. J. A. Jayalal
National President
IMA

Dr. Ravi Wankhedkar
Past National IMA President
Co-ordinator

Dr. Jayesh Lele
Hony. Secretary General
IMA HQ

Dr. Ramkrishna Londhe
President
IMA MS

Dr. Ashok Adhao
Past National
IMA President

Dr. Milind Naik
Past National
IMA Vice President

Dr. Pankaj Bandarkar
Hon. Secretary
IMA MS

Compiled by

Dr. Sanjay Deotale
President
IMA, Nagpur

Dr. Prashant Nikhade
Chairman
Mucormycosis District Task Force
Nagpur, Maharashtra

Dr. Sachin Gathe
Hon. Secretary
IMA, Nagpur

Dr. Ashish Disawal
Vice Chairman
HBI, IMA MS

Dr. Avinash Wase
Past President
IMA, Nagpur

Dr. Samir Thakare
Hon. Secretary
Vidarbha AOI

Dear IMAites,

Greetings,

I am grateful to our beloved National President Dr. J. A. Jayalal Sir, Hon. Secretary General Dr. Jayesh Lele Sir for giving me this opportunity to share some useful information about the dreaded fungal infection, Mucormycosis.

I am indebted to Dr. Ravi Wankhedkar Sir, Past National IMA President; Dr. Ashok Adhao Sir, Past National IMA President; Dr. Milind Naik Sir, Past National IMA Vice President; Dr. Ramkrishna Londhe, President, IMA MS; & Dr. Pankaj Bandarkar, Hon. Secretary, IMA MS for encouraging and motivating me to come up with these guidelines.

I sincerely thank Dr. Sanjay Deotale, President, IMA, Nagpur; Dr. Sachin Gathe, Hon. Secretary, IMA, Nagpur; Dr. Vijayalaxmi Shinde, MBBS, MD Microbiology, Eva Women's Clinic and Lab, Dombivali; Dr. Avinash Wase, MBBS, MD Pathology, Imm. Past President Vidarbha Association of Pathologist & Microbiologist, Nagpur; Dr. Ashish Disawal, Vice Chairman, HBI IMA MS; Dr. Samir Thakare, Secretary, Vidarbha AOI for their contribution and help.

Hope these guidelines will help all of us to diagnose and manage this potentially lethal fungal disease effectively at an early stage.

Be Safe. Take Care!

Regards!

Jai IMA!

Dr. Prashant Nikhade
Chairman
Mucormycosis District Task Force
Nagpur, Maharashtra

MUCORMYCOSIS

Fungi are the interface organisms between Life and Death - Paul Stamets

Fungal infections are most commonly associated with immunocompromised individuals. Fungal infections can be localized, systemic and invasive. Fungal infection can also have a nosocomial etiology.

Since the onset of the COVID-19 pandemic there have been multiple reports across country of very high incidence of mucormycosis (also called as zygomycosis) amongst patients with COVID-19 especially in those who are diabetic and those who have received steroids. COVID-19 Associated Mucormycosis (CAM) has been associated with high morbidity and mortality, exorbitant treatment costs and has led to shortage of antifungal drugs.

Mucormycosis is a dreaded fungal infection that mainly affects people on medication for other health problems that reduces their ability to fight environmental pathogens. It may turn fatal if uncared for. It is not a black fungus, the necrosis which it causes gives rise to black discolouration to the area involved.

AETIOLOGY

Caused by Fungus Rhizopus and Mucor of the order Mucorales mainly.

AGE / SEX

No predilection

ACQUIRED BY

Inhalation of ubiquitous spores (air borne)

AFFECTS

Mostly Paranasal Air Sinuses, Lungs, Cutaneous, Gastrointestinal, Disseminated get affected after inhalation of fungal spores from the air. It is non contagious in nature.

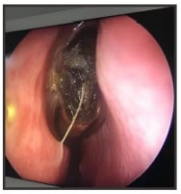
PREDISPOSING FACTORS

- Uncontrolled Diabetes Mellitus
- Immunosuppression by Steroids
- Prolonged ICU Stay (reused face masks for oxygen delivery, reused tubing's, unhygienically prepared swab sticks = direct inoculation)
- Co-morbidities - Post transplant / Malignancy

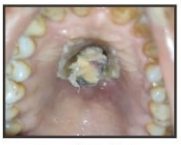
SIGNS AND SYMPTOMS

Rhino-orbital Involvement

- Initially nasal blockage or congestion, foul smell
- Nasal discharge - Non purulent but rather thin and occasionally blood - streaked. With time the infection progresses relentlessly to the contiguous tissues including the Orbit. Erythematous to violaceous to black necrotic eschar in nasal cavity.
- The turbinates or hard palate develops black, friable areas. Exposed palatal bone, sinus tract, halitosis.
- Facial Pain, Numbness and Redness around eyes and / or nose, sinus tract on face.
- Fever

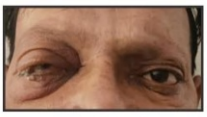


Nasal Endoscopy

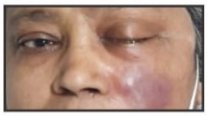


Hard Palate

- Headache, Orbital pain.
- Blurred or double vision with pain, paresthesia.



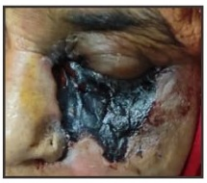
Orbital



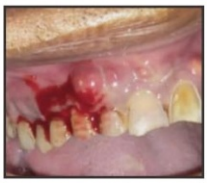
Orbital

Teeth Involvement

- Toothache, Loosening of maxillary teeth, Jaw involvement, Swollen, infected gums.



Orbital (Eschar)



Teeth

Skin Involvement

- Thrombosis and Necrosis (Eschar), Discoloration of skin.

Pulmonary Involvement - A pulmonary and disseminated form may occur.

- Cough
- Shortness of Breath
- Chest pain
- Pleural effusion
- Haemoptysis

Cerebral Involvement - Without treatment the Frontal and Temporal lobes of the Brain, the Cavernous sinus and the other adjacent structures are involved

- Altered Mental status
- Focal seizures
- Cranial nerve involvement

WHEN TO SUSPECT - (In COVID-19 patients, diabetics, immuno suppressed individuals)

- Nasal Blockage or congestion, Nasal Discharge (blackish / bloody)
- One sided facial pain, Numbness or swelling, Headache
- Blackish discoloration over bridge of nose / palate
- Toothache, loosening of maxillary teeth, jaw involvement, swollen, infected gums
- Blurred or double vision with pain, fever, skin lesion (thrombosis and necrosis - eschar formation)
- Chest pain, pleural effusion, haemoptysis, worsening of respiratory symptoms

MANAGEMENT

Mucormycosis is a medical emergency even when clinically suspected

INVESTIGATIONS

- ***LAB PARAMETERS*** - CBC, ESR, FBS PPBS, HbA1C, LFT, RFT with electrolytes, HIV, HbsAg, CSF (If indicated)
- ***NASAL ENDOSCOPIC EXAMINATION*** - Black, necrotic eschar tissue.
- ***MICROBIOLOGY*** - It is important to diagnose fungal infection early. Common pathogenic fungi in respiratory system, paranasal sinuses, ocular infections are caused by filamentous mould like fungi Mucor (zygomyces), aspergillus etc. Some dermatitious fungi are also known to cause ocular, paranasal sinus infection. Fungi causing sepsis or localized infection are common pathogenic Candida species. There is a different group of fungi causing skin, nail, hair infections like the dermatophytes, cutaneous fungi etc.

- **Lab Diagnosis** Sample - Sputum, tissue, blood, pus, fluid, appropriate lesion etc. Appropriate collection - Avoid mixing any unsterile saline or fluids in sample. Avoid contamination of sample. Strictly no formalin for fungal culture. Avoid swab stick if possible (less material, cotton absorbs material and its fibres interfere). Send samples in sterile container only. Tissue specimens more desirable.

  Direct Microscopy by KOH mount and Gram stain commonly done. (Specialized fluorescent stains available at few labs only)

  Fungal Culture - Is preferred choice standard for diagnosis for common yeast like and filamentous mould like fungi. Reporting time for fungal culture varies from 3 days to 3 weeks. Some serological tests do exist which are commonly done in tertiary laboratories only.

  Molecular Identification - PCR (fresh sample needed)

- **Sample Collection :**

  Rhino-orbito-cerebral - Consult ENT surgeon for endoscopic collection of debrided tissue / biopsy one portion in sterile water for microscopy and culture, other portion in formol saline for histopathology.

  Pulmonary - Broncho alveolar lavage (BAL), mini BAL, non bronchoscopic lavage, transbronchial biopsy, CT guided biopsy from lung - process for microscopy and culture.

  Fungal multiplex PCR are also done in tertiary laboratories and hospitals. It is important to correlate clinically and send appropriate adequate sample for fungal cultures. Molecular diagnostics have about 75% sensitivity and can be used for confirmation of diagnosis where available.

  Diagnosed with difficulty, the fungi are characterized by ribbon like hyphae that are 6 to 50 μ wide, rarely separate and have a tendency to branch at right angles.

PATHOLOGY - Histopathology also plays an important role in diagnosis. The tissue sample can range from nasal / sinus mucosa, turbinectomy, partial maxillectomy, alveolectomy, partial and total palatal resection, total maxillectomy with orbital exenteration. After proper grossing, tissue is subjected for formalin processing. Bone is decalcified. The histological findings include ulceration of mucosa, infarctoid necrosis .The Necrosis is prominent and it is accounted for by the propensity of hyphae to proliferate within smaller blood vessels producing thromboses. Non septate fungal hyphae infiltrating tissue, vessel, nerve or as balls over surface. Extensive inflammation and foreign body giant cell reaction, infarctoid necrosis of bone. 10% formalin is used as preservative for biopsies. Rapid diagnostic techniques such as **frozen section, squash and imprint** are very much useful if available.

RADIOLOGY - Suspected patients should undergo appropriate radio imaging study.

- **Tomograms :** are useful in delineating the extent of disease. Contrast enhanced CT scan with 3D reconstruction findings: Erosion and thinning of Hard Palate, Mucosal thickening of Sinuses with irregular patchy enhancement is an early sign, Enlargement of masticator muscle, changes in fat planes.
- **MRI-PNS :** Ischaemia and nonenhancement of turbinates manifests as an early sentinel sign on MRI - **Black turbinate Sign.** The **fluid level** in the sinus and partial or complete sinus opacification signifies advanced involvement of paranasal sinus. Thickening of the medial rectus is an early sign of orbital invasion. Patchy enhancement of orbital fat, lesion in the area of superior and inferior orbital fissure and the orbital apex and bone destruction at the paranasal

sinus and orbit indicate advanced disease. Stretching of the optic nerve and tenting of posterior pole of the eyeball indicate severe inflammatory oedema secondary to tissue necrosis.

MRI-PNS with Brain contrast study - MRI and MR angiography help to determine the extent of Cavernous sinus involvement, Ischaemic changes to the CNS, Optic neuritis, Infra temporal fossa involvement.

- **Pulmonary - Lung CT :** Confused with COVID related shadows, suspect mucormycosis in patients with thick walled lung cavity (need to differentiate from COVID associated pulmonary aspergillosis), reverse halo sign, multiple nodules, pleural effusion.

Do's

- Control hyperglycemia (Sugar Control).
- Monitor Blood Glucose level post COVID 19 discharge and also in diabetics.
- **USE STEROIDS JUDICIOUSLY -** correct timing, correct dose and duration.
- Use Clean, sterile water for humidifiers during Oxygen therapy.
- Use Antibiotics / antifungals judiciously.

Don'ts

- Do not miss warning signs and symptoms.
- Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators.
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining and microscopy, culture) for detecting fungal etiology.
- Do not lose crucial time to initiate treatment for mucormycosis.

TREATMENT

Team approach is required with Infectious Disease Specialist, Microbiologist, Histopathologist, Intensivist, Neurologist, ENT Specialist, Ophthalmologist, Dentist, Surgeons (Maxillofacial, Plastic), Radiologist, Biochemists etc.

- Control Diabetes and Diabetic Keto acidosis
- Reduce steroids (If patient is still on) with aim to discontinue rapidly
- Discontinue immunomodulating drugs.

MEDICAL TREATMENT

- Insert peripherally inserted central catheter (PICC line)
- Maintain adequate systemic hydration
- Infuse normal saline IV before Amphotericin B infusion
- Antifungal therapy for at least 4-6 weeks

First Line

1. **Liposomal amphotericin B (L-AmB)** (Preferred treatment)

   5 mg / kg / day, dilute in 200 cc 5% dextrose over 2-3 hours infusion (avoid slow escalation) higher dose 7.5 mg to 10 mg / kg / day may be given in Brain involvement.

   Advantage : Less nephrotoxic , Better CNS penetration

   Disadvantage : Expensive

2. **Inj. Amphotericin B Deoxycholate (D-AmB)** (if cost and availability of L-AmB is an issue)

   1 mg / kg / day in 5% dextrose, slow infusion for 6-8 hours.

   Pre-medication : (NSAID and/or diphenhydramine or acetaminophen with diphenhydramine or hydrocortisone, Pre infusion administration of 500 to 1000 ml of normal saline may be required to avoid infusion reaction.

   Disadvantages - Highly toxic, poor CNS penetration

3. **Inj. Amphotericin B Lipid Complex (ABLC) -**

   5 mg / kg / day

   Advantage : less nephrotoxic than D-AmB

   Disadvantage : Expensive, Possibly less effective than LAmB for CNS infection.

4. Monitor Renal function and Potassium level while treating with Amphotericin B
5. Patients who are intolerant to Amphotericin B , alternative agents are posaconazole or isavuvonazole (Injection/Tablet)

Second Line -Azole derivatives

6. Tab Posaconazole delayed release tablets300mg twice a day on first day, followed by 300 mg once a day taken with food. Check posaconazole trough level after 7 days of therapy and avoid interacting drugs.
7. Tab Isavucanazole; 200 mg three times a day for two days followed by 200 mg once a day.

   Monitor patients clinically, with radio-imaging, for response / disease progression and microbiologically.

   After 3-6 weeks of amphotericin B therapy, consolidated therapy (Posaconazole / isavuconazole) for 3-6 months.

SURGICAL DEBRIDEMENT

Extensive surgery is needed to remove all necrotic material.

Endoscopic Sinus surgery, Turbinectomy, Maxillectomy (Partial or Total), Zygoma Debridement, Debridement of Orbital Floor / Walls plus localised debridement of necrosed tissue in early localized orbital disease, Exenteration of eye, Anterior table debridement, Posterior table cranialisation, Debridement of osteomyelitic skull bone.

It is a teamwork involving ENT Surgeon, Maxillo-facial Surgeon, Plastic surgeon, Ophthalmologist, Neurosurgeon, Anaesthesiologist, Intensivist.

Patients would need to come to terms with loss of function due to a missing jaw, difficulty in chewing, swallowing, facial aesthetics and loss of self esteem. Be it the eye or the upper jaw, these can be replaced with appropriate artificial substitutes or prostheses. It is important to reassure patient about the availability of such interventions instead of leaving him to panic with sudden unforeseen loss augmenting a post-COVID stress disorder which is already a reality. Prosthetic reconstruction can be effected after surgery but interim solutions should be planned even before surgery for better outcome.

PREVENTIVE MEASURES

- Use Masks - (if you are visiting dusty construction sites) in potential infective environment.
- Frequent cleaning of premises.
- Prefer disposables in patient care areas.
- Isolation advised for hospitalized patients.
- Monitoring of Infection Prevention & Control practices in High Risk Units.
- Wise, restricted, supervised use of Antibiotics, antifungal and immunomodulator drugs, immunosuppressive drugs. Systemic steroids are to be used in patients with hypoxia and oral steroids should be avoided in patients with normal oxygen saturation on room air. If systemic steroids are used, blood sugar should be monitored. The dose and duration of steroid therapy should be limited to Dexamethasone (0.1 mg/kg/day) for 5-10 days.
- Aggressive monitoring and control of diabetes mellitus, good glycemic control (110-180mg/dl) during management of COVID-19 patients is required.
- Strict aseptic precautions while administering oxygen (sterile water for humidifier)
- Complete ENT Evaluation periodically (Day 1 & between day 3 to7)
- Complete Ophthalmological Evaluation periodically (Day 1 & between day 3 to7)
- Radiological Evaluation in very high clinical suspicious patients.
- Wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure.
- Maintain Personal Hygiene including thorough Scrub Bath. Hand hygiene.
- While discharging patients from hospital, counselling about early signs and symptoms of mucormycosis (one sided Facial Pain and swelling or numbness, nasal blockage, nasal discharge, headache, pain in the eye, toothache, loosening of teeth, discomfort during chewing, swelling of eye, double or blurred vision, chest pain, respiratory insufficiency) should be done.

REMEMBER

Mucormycosis is not contagious. It does not spread from one person to other. The fungi remain in the outdoor and indoor environment. The spores enter the respiratory tract via air.

No antifungal prophylaxis is recommended as the incidence is not more than 10% in any COVID-19 cohort.

With advent of newer molecules in medical management and better instruments and infra-structural facilities the outcome of mucor treatment has taken a paradigm shift.

Covid 19 is here to stay. We need to find out ways and means to live with it. Be Safe. Take Care!

Friends,

I have considered important recommendations issued by ICMR; Fungal Infection Study Forum (FISF); Indian Journal of Ophthalmology; Expert Committee of Civil Hospital, Ahmedabad; Study Group, Sir Ganga Ram Hospital, New Delhi; from time to time while compiling these guidelines.

Regards!

Dr. Prashant Nikhade
Chairman, Mucormycosis
District Task Force, Nagpur, Maharashtra

Dr. J.A. Jayalal
National President, IMA

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

To,
All Members of IMA

Sub : **Information regarding 18th June 2021 – IMA Protest Day**

Dear Colleagues and Leaders,

Warm Greetings from Indian Medical Association (Hqs.)!

First of all, we salute and pay homage to 700 of our colleagues who have died during the second wave of pandemic and also greet you for all your exemplary services to mitigate Covid disaster from the front line.

It is painful to note that Mr. Ramdev, a Yoga Instructor with substantial following in public domain and having vested interests in his business fortunes, choose to spit out acerbic language on our evidence based modern medicine professionals at a time when the country is passing through a medical emergency.

Because of our unity, strength and advocacy role, Mr. Ramdev was compelled to publically issue the statement saying that "DOCTROS ARE DEVDOOTS" and he will personally also go for vaccination. But the mental agony/verbal violence inflected on us, is unforgettable. We thank our Honourable Prime Minister, was making it clear anyone acts against vaccination is doing harm to nation, has set the tone for this. And IMA appeal to Prime Minster for appropriate actions to prevent such incidence.

Equally, we are pained to see the unleash of series of violence on doctors on Covid duty in the last two weeks in Assam, Bihar, West Bengal, Delhi, UP, Karnataka and many other places. Doctors have sustained multiple fractures and serious injuries and female doctors face more violent verbal and physical assaults. Every day it is happening. We have tried our best to bring these distressing acts to the notice of Honourable Prime Minister, Honourable Home Minister, Honourable Health Minister and the Hon'ble Chief Ministers of various States but of not much relief. We thanked Assam Chief Minister for his care and concern shown to the affected Doctors.

We need to express our anguish and solidarity to make the Government realize and come out in public and ensure: -

1. Central Hospital and Health Care Professionals Protection Act with IPC & CrPC tag
2. Standardization and augmentation of security in each hospital.
3. Hospital shall be declared as protected zone.
4. Assault culprits shall be punished under fast-track mode and stringent punishment shall be given.

As a responsible organization, we are conscious of our duties during this pandemic times. Action Committee of IMA, after considering all the aspects and to express our concern, anger and solidarity, have decided to observe the 18th June 2021 as IMA National Protest Day with objective of "to stop assault on profession and professionals" with the slogan "Save the Saviours".

As a prelude June 15th will be observed as National Demand Day and Press Meet will held across the country by branches. A video of our good works shall be release and along with the data of vaccines assaults taken place in your areas, without personal identification.

On behalf of IMA HQs, we are requesting you to conduct the following programmes with all your passion and involvements for the successful observance of the above Protest Day – Save the Saviours on June 18th:

1. Wear Black Badges, Flags, Masks, Ribbons, Shirts etc.
2. Banners, carry placards with slogan "Save the Saviours" and "Stop Violence on Profession and Professionals".
3. Protests to be organized at IMA Buildings or prominent places in your city and infront of each hospital along with healthcare workers.
4. Mass Petition against the assault on medical profession and Professionals to be sent to the Prime Minister of India (copy enclosed).
5. The public awareness meetings with leaders of the society, colleagues of other profession, opinion builders and administrators, NGOs be held to plan an action group to mitigate the violence in hospital.
6. Medical students Conclave, a comprehensive representation of students from each medical college shall be conducted in every state and boycott the online classes.
7. Press Conferences to be organized with social media and print media.
8. Lobbying with Administrative/political leaders.
9. Submit the video/photo in Whatsapp and send to Dr. Jayesh Lele, HSG and state office.

Memorandum of our demands should be submitted to the Local SSP/DM, MLAs and MPs of your area / districts.

IMA (Hqs.) will send the design of banner, badges and the format of letter to Hon'ble Prime Minister of India.

We are having enough time to motivate to bring together everyone and ensure that everyone is involved. Feel free to contact us for any further help.

We are sure with our united efforts; we will be able to successfully project our demands to the Government. This is a beginning of our struggle to reach our goal of safe environment and protection to our profession.

Dr. J A Jayalal
National President

Dr. Jayesh M Lele
Honorary Secretary General

INDIAN MEDICAL ASSOCIATION (HQs.)

(Registered under the Societies Act XXI of 1860)
Mutually Affiliated with the British & Nepal Medical Associations
I.M.A. House, Indraprastha Marg, New Delhi-110 002
Telephones: +91-11-2337 0009 (10 lines), 23378680 / +91-9999116375, 9999116376, Fax: +91-11-23379470
Website: www.ima-india.org ; Email: hsg@ima-india.org

National President	Immediate Past National President	Honorary Secretary General	Honorary Finance Secretary
Dr. J A Jayalal	**Dr. Rajan Sharma**	**Dr. Jayesh M Lele**	**Dr. Anil Goyal**
(M): 9443160026	(M): 9812054730	(M): 9819812996	(M): 9811101454
Email: lapsurgeon2001@yahoo.co.in	Email: rajanhospital@gmail.com	Email: drjayeshlele@gmail.com	Email: drgoyalhospital@gmail.com

07.06.2021, New Delhi

To,
The Hon'ble Prime Minister
Government of India

Sub: Appealing for your personal intervention to resolve the long pending pleas of the Indian Medical Association and to ensure optimum milieu for Modern Medical professionals to work with compassion and dedication, without mental and physical fear.

Beloved Honourable Prime Minister Ji,

IMA is the largest professional association of Modern Medical professionals in India ever since its inception in 1928 by Indian Doctors including Dr. K. S. Ray, Sir Nil Ratan Sircar, Dr. B. C. Roy, Dr. M. A. Ansari, Col. Bhola Nath, Major M. G. Naidu, Dr. B.N. Vyas, Dr. D. Silva, Dr. N. A. Ghosh, Dr. D. A. Chakravarthi, Dr. Viswanathan, and Capt. B. V. Mukherjee who had also actively participated in the struggle for Independence of the country. The IMA has been constantly striving towards fulfilling its objectives of Promotion and Advancement of Medical and Allied Sciences in all their different branches, the improvement of Public Health and Medical Education in India and the maintenance of honour and dignity of medical profession.

During the ongoing COVID-19 pandemic, the entire medical fraternity, right from day one, has been battling at the frontlines in the war against coronavirus and has been able to save millions of people from the clutches of severe COVID-19 infection and in the bargain, it has lost more than 1400 of its proactive veterans and dynamic younger ones as martyrs in this war against COVID-19.

On behalf of the Indian Medical Association representing the collective consciousness of more than 3,00,000 front line warriors at the COVID-19 care front line, we express our gratitude for your exemplary leadership and altruism in this pandemic. Though the second wave has stuck our country very severely and has made our people to suffer, your innovative steps to augment oxygen supply, encourage judicious use of Remdesivir and expedite enhancement of hospital beds and capacity have enabled the frontline workers to work with dedication towards reducing the mortality rate of this deadly virus.

We believe that it is your proactive innovation of rolling out vaccination which is solely instrumental in safeguarding thousands of persons from being victims of corona and protecting them against the severe symptoms of the disease. IMA, right from day one, has been proactively standing with the Government to encourage, endorse and augment the vaccination drive in the nation. With your patronage, the vaccine hesitancy in the minds of the common public has substantially reduced.

However, we are very much anguished and pained to once again bring to your kind notice the continuing attempts of certain people to propagate the disbelief and misinformation in relation to the vaccines and the evidence based scientific protocols of Modern Medicine released from time to time by the Ministry of Health, Government of India along with the guidance of ICMR and the Covid-19 Task Force.

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I.M.A. House, Indraprastha Marg, New Delhi-110 002
Telephones: +91-11-2337 0009 (10 lines), 23378680 / +91-9999116375, 9999116376, Fax: +91-11-23379470
Website: www.ima-india.org ; Email: hsg@ima-india.org

National President	Immediate Past National President	Honorary Secretary General	Honorary Finance Secretary
Dr. J A Jayalal	**Dr. Rajan Sharma**	**Dr. Jayesh M Lele**	**Dr. Anil Goyal**
(M): 9443160026	(M): 9812054730	(M): 9819812996	(M): 9811101454
Email: lapsurgeon2001@yahoo.co.in	Email: rajanhospital@gmail.com	Email: drjayeshlele@gmail.com	Email: drgoyalhospital@gmail.com

In the midst of this pandemic, we are also deeply hurt to see the increasing incidents of physical violence against the doctors and the health care professionals in this country. The brutal assault on our young Doctor in Assam and the assault on lady doctors and even on veteran practitioners across the country - are really causing mental trauma amongst the practitioners.

Many young doctors have also lost their lives on account of their dedicated service to thousands of people – which has affected not only the Doctors but also many of their close family members. There are cases where both husband and wife being doctors have lost their lives, leaving behind their children as orphans. IMA is maintaining a registry of all such cases, and we periodically submit these details to the authorities seeking recognition and support for these families.

With the continuous and ongoing physical and mental assault on our doctors as well as purposeful spread of misinformation against modern medicine and vaccination by certain people with vested interests – IMA is constrained to once again appeal to you to personally intervene and resolve our long pending pleas including the following:-

1. Any person(s) who spreads misinformation against the vaccination drive which is meant to fight the COVID-19 pandemic, must be booked and punished in accordance with law including under the relevant provisions of the Epidemic Diseases Act, 1897, the Indian Penal Code and the Disaster Management Act, 2005. All such acts of omission and commission on behalf of any person raising doubts in the minds of the common public against the protocol guidance issued by Ministry of Health for treatment of COVID-19 infected patients – ought to be suitable punished and simultaneously, any attempt of any person to fool the gullible public and promote so-called “magic remedies” or “wonder drugs” without the approval of the Ministry of Health, Government of India – ought to be immediately curtailed.

2. The Health Services Personnel and Clinical Establishments (Prohibition of Violence and Damage to Property) Bill, 2019, which seeks to punish people who assault on-duty doctors and other healthcare professionals by imposing a jail term of up to 10 years – which, apparently, was dismissed by the Home Ministry during an inter-ministerial consultation over the draft law, ought to be promulgated immediately alongwith the incorporation of provisions from the IPC / CrPC and with stipulations for a fixed time schedule for speedy conclusion of trials. All those involved in such heinous crimes ought to be punished so as to also create an effective deterrent for other antisocial elements who may indulge in attacking any Health care professionals.

3. The doctors who have lost their lives in the war against the COVID-19 pandemic ought to be recognised as COVID MARTYRS with due acknowledgment of their sacrifice. Their families ought to be duly supported by the Government. We thank you for the Pradhan Mantri Garib Kalyan Yojana scheme under which insurance benefits are being extended to such families, however, we wish to bring to your kind notice that due to various obstacles in the procedural implementation of the Scheme, out of 754 doctors who had lost their lives in the first wave, families of only 168 Doctors have been able to apply under this Scheme. IMA requests you to create an effective mechanism for identifying and verifying all these victims

INDIAN MEDICAL ASSOCIATION (HQs.)

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I.M.A. House, Indraprastha Marg, New Delhi-110 002
Telephones: +91-11-2337 0009 (10 lines), 23378680 / +91-9999116375, 9999116376, Fax: +91-11-23379470
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Email: lapsurgeon2001@yahoo.co.in	Email: rajanhospital@gmail.com	Email: drjayeshlele@gmail.com	Email: drgoyalhospital@gmail.com

through the Central Bureau of Health Intelligence (CBHI) and also ensure that the support shall be given to all the said families as solatium at their door steps

4. IMA believes that vaccination is the only weapon to promote and empower our country to get over the pandemic and to protect our vulnerable population. It is gratifying to note that only .06 % of people who have received both the doses of vaccine got minimal infection by a coronavirus, and very rarely did vaccinated people have any severe infection. It is well proved, that by vaccination we can save our people and country from the catastrophic cascades of this severe infection. Even worldwide, vaccination has been found to be the most effective solution to tackle the coronavirus pandemic and prevent the loss of lives to the maximum extent possible. Hence, the Government should promote universal free vaccination to all above 18 years of age without leaving the vaccines to the extent of 50% to the states and private hospitals. We believe that only when a strong leader like you leads this programme, the full benefit shall reach out to all people.

5. The post COVID-19 complications of lung fibrosis, increased thrombotic events and fungal infections are on the rise and we need to get prepared for the same. The drugs needed for the mucormycosis fungal disease are not available with ease and we thank you for the efforts taken to import the said drugs and simultaneously augment indigenous production. We appeal to you to set up a separate research cell to study these post COVID-19 complication in detail and to come out with multifaceted treatment guidelines in all disciplines of Medicine.

Sir, IMA has decided to continue to seek your intervention on the above issues and also to organise various intellectual meets, dialogues, and finally the NATIONAL PROTEST DAY on 18th June to secure smooth, cooperative and optimum milieu for Modern health care professionals which will enable them to work with much more compassion and dedication and without any fear of mental or physical harm.

We are humbly awaiting your personal intervention for resolving all of our above mentioned pleas.

Thanking you.

Dr. J A Jayalal
National President

Dr. Jayesh M Lele
Honorary Secretary General

OFFICE OF THE PRESIDENT
THE ASSOCIATION OF PHYSICIANS OF INDIA

Dr. Kamlesh Tewary
MD. FRCP (Glasgow), FRCP (Edin.) FICP, FIACM, FIAMS
President: - Association of Physicians of India (2021-22)
Ex. Prof. & HOD Medicine, S. K. Medical College, Muzaffarpur, Bihar

Dr. Mangesh Tiwaskar
Hon.General Secretary

Date: 16-06-2021 **Modified**

सूचना

चिकित्सकों पर हो रहे हिंसा की घटनाएँ एवं श्री रामदेव के द्वारा आधुनिक चिकित्सा विज्ञान, पद्धति, कोविड टीकाकरण एवं शहीद चिकित्सकों के खिलाफ दिये गये वक्तव्य के विरोध मे राष्ट्रीय आई. एम.ए. के आह्वाहन पर दिनांक 18 जून 2021 (शुक्रवार) को सुबह 08:30 बजे से 12:30 बजे तक ओ.पी.डी. सेवाएँ बंद रहेगी।

We endorse the call of IMA and request our members to follow this.

We would further request to upload pictures of their protest on our website / whatsApp group to show our solidarity with IMA.

1. **Covid work & Emergency- Exempted**
2. **Members also follow their respective state IMA guidelines.**
3. **Must wear black badge on 18th June 2021.**

Dr. K Tewary

Dr (Prof) K Tewary
President API (2021-22)
Phone:+91-9431239517
Email: tewarykamlesh@gmail.com, drktewary@yahoo.co.in

Physical assault and mental abuse of doctors has gained the proportion of an epidemic. Traditionally we have embarked upon a “forget and forgive" attitude. But the increasing assault against these professionals “ who have risked their lives since March 2020”have reached a disproportionate height. It is time, therefore, to call for an attitude of “zero tolerance" from this date onwards.

Prof Dr Diptendra K Sarkar
IPP, Association of Breast Surgeons of India
VP, Association of Surgeons of India, WB chapter

Dr. Kaushik Ranjan Das
President
Geriatric Society of India®

To,
Prof.(Dr.) J.A. Jayalal
National President IMA

Dr. Jayesh M. Lele
Honorary General Secretary IMA

Respected Dr. Jayalal & Dr. Lele
Greetings from Geriatric Society Of India.

The Geriatric Society of India finds the rising violence against doctors as unaccepted, serious and extremely disturbing.
On behalf of Geriatric Society of India , myself(The President ,GSI) express our deep concern and express our full support and solidarity toward the protest of “Indian Medical Association”(IMA) on 18th June 2021 to observe this day as National Protest Day with the slogan of “Save The Saviours” against assault on doctors.

Stringent action against the perpetrator backed by appropriate law with exemplary punishment can make the prevailing situation congenial to service delivery.

Long Live Doctors Unity

Warm Regards
(Dr. Kaushik Ranjan Das)
President
Geriatric Society of India®

Date: 17.06.2021

VIOLENCE AGAINST PHYSICIANS IN INDIA

WMA strongly condemns any sort of violence against health care professionals. There is rising trend globally for violence against physicians and health care facilities. Violence against physician or nurses is basically a violence against patients. The recent incident in India highlights the gravity of situation. The WMA urges all the sections of society not to tolerate such acts. We support the initiatives of Indian Medical Association to curb this menace and request all the member organizations to advocate for a safe working environment for those who work in health care.

Zero tolerance to any kind of violence in healthcare! WMA

The Association of Surgeons of India

(Regd. No. 20 of 1940-41 Under Tamil Nadu Registration of Societies Act XXI of 1860)
No. 18, Adams Road, Chepauk, Chennai - 600 005, INDIA.
Phone : +91 - 44 - 25383459 / 25381685 / 25385584 / 25367095
E-mail : headoffice@asiindia.org Website : www.asiindia.org

15th June 2021

With start of the unfortunate pandemic that hit the World in March 2020, an appeal was made to essential services including medical fraternity to help manage COVID hit patients. With obvious fear in mind but remembering the Hippocrates oath, doctors from all specialties rose to the occasion and fought tooth and nail despite hardships and even deaths.

Association of Surgeons of India (ASI) is the largest body of Surgeons consisting 27725+ members. The Association in the year 2020 donated PPE kits, sanitizers and other items amounting to more than a crore of rupees all over the Country. With this deadly second wave that has been even more lethal coupled with black fungal superinfection, surgeons and postgraduate trainees are relentlessly working to prevent spread and treating COVID patients 24x7.

While the patience of general population seems running out, the doctor community including the surgeon members of this Association has raised apprehension of violence against them or filing of cases of negligence against them. It is our duty to ask the concerned authorities.to ensure non-violence against the doctor-surgeons as well as provide immunity against legal actions that may be initiated against them.

The Association of Surgeons of India strongly supports the Indian Medical Association who has raised these fears amongst doctors and requests protection to the doctors against violence and also provide legal immunity while treating COVID patients.

Sincerely

Dr. Abhay Dalvi
President

Dr. Sanjay Kumar Jain
Hon Secretary

INDIAN RADIOLOGICAL & IMAGING ASSOCIATION

Year 2021

Registered Under "Registration of Societies Act XXI of 1860" Vide Registration No. 6644 Dated: 30.03.1937
Registered Office: 6, Park Side Road, Kolkata-700026

Secretariat: IRIA House, C-5, Qutab Institutional Area, New Delhi -110 016
Tel. +91-11-26965598, +91-11-41688846, Fax: +91-11-26565391
E-mail: iria37@gmail.com; Website: www.iria.org.in

PRESIDENT
Dr. C. Amarnath
CCB 026, 2nd Floor, Door No. 6
Commanders Court, B Block
49, Ethiraj Salai, Egmore
Chennai - 600008
Mobile: +91 9884877622
Email: amarrd02@yahoo.co.in

SECRETARY GENERAL:
Dr. Sandeep Kavthale
Vision Diagnostic Centre
R-3, 1058, Tilak Nagar
Latur -413512
Mobile: +91 8888595555
Email: sandeepkavthale@gmail.com

PRESIDENT ELECT
Dr. Pushpraj Bhatele
353, Nehru Nagar, Near Apex Hospital
Opp. Medical College
Jabalpur- 482003
Mobile: +91 9826155786
Email: drprbhatele@gmail.com

IMMEDIATE PAST PRESIDENT
Dr. Deepak Patkar
10, Laxmi Mahal
Bomanji Petit Street, Warden Road
Mumbai-400 036
Mobile: +91 9821136677
Email: drdppatkar@gmail.com

VICE PRESIDENTS:
Dr. Sampangi Ramaiah S. (Bengaluru)
Mobile: +91 9845218599
Email: drsampangi@gmail.com

Dr. Akhilesh Sharma (Kanpur)
Mobile: +91 9839086990
Email: akhilesh_cam@yahoo.co.in

HON TREASURER:
Dr. Pankaj Sharma (New Delhi)
Mobile: +91 9910661497
Email: pankajrad7477@yahoo.com

JOINT SECRETARIES:
Dr. Pranabananda Goswami (Kolkata)
Mobile: +91 9830024193
Email: goswami.drpranabananda@gmail.com

Dr. Aniruddha Kulkarni (Aurangabad)
Mobile: +91 9822321213
Email: drark123@gmail.com

ADMINISTRATIVE OFFICER:
Harish Saryal
Mobile: +91 9818079880

June 17, 2021

To,

Prof. (Dr.) J. A. Jayalal
National President, IMA

Dr. Jayesh M. Lele
Honorary Secretary General, IMA

Dear Dr. Jayalal & Dr. Lele,

Greetings from IRIA!

The ‘Indian Radiological & Imaging Association’ (IRIA) finds the violence against doctors extremely serious and disturbing.

The ‘Indian Radiological & Imaging Association’ expresses its concern and expresses its full support and solidarity on the protest of ‘Indian Medical Association’ (IMA) on 18th June 2021 to observe this day as National Protest Day with the slogan of ‘Save the Saviors’ against assault on doctors.

There must be strict implementation of central hospital and Health Care Professionals Protection Act with IPC and Code of Criminal Procedure (CrPC), standardization and augmentation of security in each Hospital/ Medical Centre and declaring Hospitals/Medical Centers as protected zones among others.

With best regards,

Yours sincerely,

(Dr. Prof. C. Amarnath)
President, IRIA

(Dr. Pushpraj Bhatele)
President Elect, IRIA

(Dr. Sandeep Kavthale)
Secretary General, IRIA

Save her. She holds the future. The sages have said, “Where women are revered, the Gods abode.”

Message from
Dr. J.A. Jayalal
National President, IMA

IMA the largest professional body of Modern medicine doctors observe National protest day on June 18th demanding enactment of stringent central law and its prudent application to stop violence on profession and professionals.

With the passionate slogan of save the saviours ,across the country 3.5 lakhs members of IMA along with the specialty organizations like API,ASI,FOGSI etc and corporate hospitals health care professionals will depict it as a black protest as the token of anguish and pain on the violence leashed on hundreds of doctors across the country . It shall be the day the united voice of medical fraternity will echo with vibrancy and might to shake the corridors of power to take urgent remedial steps to create a milieu of safe and healthy environment in hospital premises for effective and dedicated services of fraternity towards of millions of people who come with distress to hospitals.

I am looking forward to see this happening before July 1st our celebrated moment of Doctors day.

Message from
Dr. Santanu Sen, MP
Past National President, IMA

Covid 19 has been a cause for global crisis for the past two years.

The people at the helm of curbing the widespread of the disease are the doctor community. Despite prolific efforts and regular unconditional sacrifices being made by the doctors, it is being noticed that Doctors are getting assaulted by common people & local goons for some filmsy reasons or no reason.

Several Doctors have already lost their lives while trying to save others and these cases are progressing with each day. Very recently two such incidents have taken place in the district of Hooghly and North 24 Paraganas. IMA reached both the places at earliest to take necessary steps. IMA Bengal started a state wide Helpline number for any violence on doctor which will be functional 24×7.

IMA has already observed a National Protest Day very successfully on 18th june with the primary agenda to raise it's voice against such atrocities. IMA further urges the Central Govt. To implement Central Act to prevent violence on Health Care Delivery System with immediate effect.

Wishing you all a good health. Long live IMA.

Dr. Santanu Sen, MP

Past National President

Hony State Secretary, IMA Bengal

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

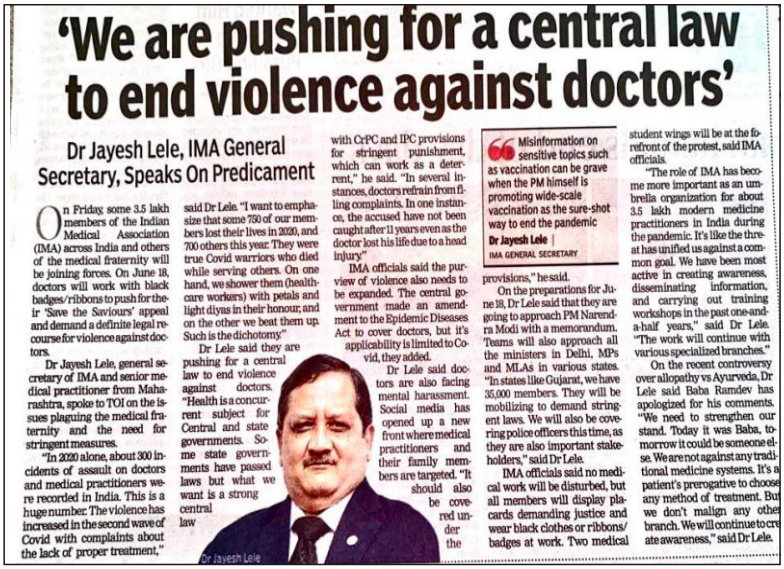
Dear Doctor ,

It gives sad feeling to write to you about the issues faced by the doctor fraternity. These days time and again we find our doctor community is in very rough times. I'm going to address to you about two major issues. We have lost nearly 1450 doctors across India, and there is no end to it. Last 18 months we are fighting war against an enemy, in the beginning it was unknown , now known but the end is not around. Our fraternity is working in adverse condition and we have saved nearly 23 Lakhs Covid patients. Death rate in India is less than many developed countries. We are also fortunate that our Indian scientists have proved their worth by formulating 2 vaccines successfully. We are ready to help the patients to fight the COVID by proper vaccination. I appeal to all our friends to donate generously so that we can help some of families who have lost their breadwinner. We are also urging Hon Prime Minister Shri Narendra Modiji to help these families.

Friends another very important issue we need to put across the Govt of India and Hon Shri Narendra Modiji, is the lond standing request about the central law in relation to Violence against Doctors and healthcare establishments. We have been talking at various levels but unfortunately we have not been able to get it.

Our 18th June IMA NATIONAL PROTEST DAY has a very good response and we are sure that all IMA members along with many medical associations will participate. It will have very good impact on media as well as govt of India. All members participation and contribution in making this protest a success is necessary, and we are sure it will energize each medical practitioner.IMA being a biggest national medical association, lot of expectations are there from others as well as the support extended to us will show the unity and strength.We congratulate all members for their continued help and support.

Long live IMA JAI HIND



'We are pushing for a central law to end violence against doctors'

Dr Jayesh Lele, IMA General Secretary, Speaks On Predicament

On Friday, some 3.5 lakh members of the Indian Medical Association (IMA) across India and others of the medical fraternity will be joining forces. On June 18, doctors will work with black badges/ribbons to push for their 'Save the Saviours' appeal and demand a definite legal recourse for violence against doctors.

Dr Jayesh Lele, general secretary of IMA and senior medical practitioner from Maharashtra, spoke to TOI on the issues plaguing the medical fraternity and the need for stringent measures.

"In 2020 alone, about 300 incidents of assault on doctors and medical practitioners were recorded in India. This is a huge number. The violence has increased in the second wave of Covid with complaints about the lack of proper treatment," said Dr Lele. "I want to emphasize that some 750 of our members lost their lives in 2020, and 700 others this year. They were true Covid warriors who died while serving others. On one hand, we shower them (healthcare workers) with petals and light diyas in their honour, and on the other we beat them up. Such is the dichotomy."

Dr Lele said they are pushing for a central law to end violence against doctors. "Health is a concurrent subject for Central and state governments. Some state governments have passed laws but what we want is a strong central law with CrPC and IPC provisions for stringent punishment, which can work as a deterrent," he said. "In several instances, doctors refrain from filing complaints. In one instance, the accused have not been caught after 11 years even as the doctor lost his life due to a head injury."

IMA officials said the purview of violence also needs to be expanded. The central government made an amendment to the Epidemic Diseases Act to cover doctors, but it's applicability is limited to Covid, they added.

Dr Lele said doctors are also facing mental harassment. Social media has opened up a new front where medical practitioners and their family members are targeted. "It should also be covered under the provisions," he said.

> Misinformation on sensitive topics such as vaccination can be grave when the PM himself is promoting wide-scale vaccination as the sure-shot way to end the pandemic
> **Dr Jayesh Lele** | IMA GENERAL SECRETARY

On the preparations for June 18, Dr Lele said that they are going to approach PM Narendra Modi with a memorandum. Teams will also approach all the ministers in Delhi, MPs and MLAs in various states. "In states like Gujarat, we have 35,000 members. They will be mobilizing to demand stringent laws. We will also be covering police officers this time, as they are also important stakeholders," said Dr Lele.

IMA officials said no medical work will be disturbed, but all members will display placards demanding justice and wear black clothes or ribbons/badges at work. Two medical student wings will be at the forefront of the protest, said IMA officials.

"The role of IMA has become more important as an umbrella organization for about 3.5 lakh modern medicine practitioners in India during the pandemic. It's like the three-a has unified us against a common goal. We have been most active in creating awareness, disseminating information, and carrying out training workshops in the past one-and-a-half years," said Dr Lele. "The work will continue with various specialized branches."

On the recent controversy over allopathy vs Ayurveda, Dr Lele said Baba Ramdev has apologized for his comments. "We need to strengthen our stand. Today it was Baba, tomorrow it could be someone else. We are not against any traditional medicine systems. It's a patient's prerogative to choose any method of treatment. But we don't malign any other branch. We will continue to create awareness," said Dr Lele.

Dr Jayesh Lele

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION :
Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phone : (033) 2237- 8092, Mobile : +919477493027; E-mail : jima1930@rediffmail.com
Website : https://onlinejima.com ; www.ima-india.org/ejima
Head office : Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones : +91-11-2337 0009, 2337 8680, Email : hsg@ima-india.org : Website : www.ima-india.org

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