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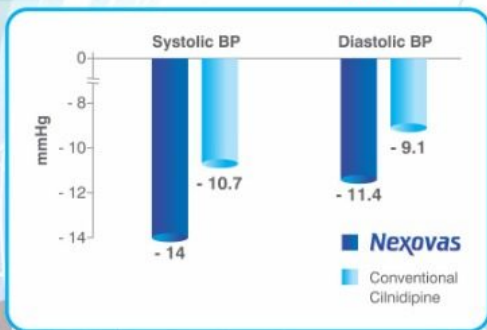
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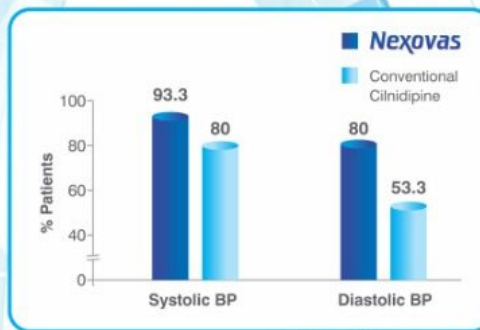


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## Antenatal Care : Quality, Utilization and Influencing Factors

### Antenatal care : Current concept :

Antenatal Care (ANC) is defined as the care provided by the skilled health care professionals to pregnant women and adolescent girls in order to ensure the best health conditions for both mother and baby during pregnancy<sup>1</sup>. The components of ANC are: risk identification, prevention and management of pregnancy-related or concurrent diseases, health education and health promotion. ANC reduces maternal and perinatal morbidity and mortality through detection and management of pregnancy-related and concurrent diseases as well as identifying individuals at increased risk of complications during pregnancy, child birth and post-partum<sup>1</sup>.

WHO envisages of a world where “every pregnant women and newborn receives quality care throughout pregnancy, child birth and post-partum period.” WHO releases comprehensive recommendations on routine ANC with positive pregnancy experience as the key consideration. A positive pregnancy experience<sup>1</sup> is defined as :

- Maintaining physical and sociocultural normality
- Maintaining a healthy pregnancy for both mother and baby
- Having an effective transition to positive labour and birth
- Achieving positive motherhood.

### Indian scenario :

In India, antenatal, intra-natal and postnatal cares are provided by both public as well as private facilities and providers. The observation of utilization of private health facilities for antenatal care by rural pregnant women in a district of Karnataka as presented by a recent study has made it imperative to take a stock of the current situation in India. It was mentioned that availability of ultrasonography and other investigations and specialists during delivery were the important factors behind choosing a private health facility over government one<sup>2</sup>.

According to National Family Health Survey (NFHS)-2019-21, Institutional delivery in public facilities has increased to 61.9% (Rural 65.3%, Urban 52.6%), compared to 52.1% during NFHS- 2015-16<sup>3-4</sup>. As per NFHS-5 (2019-21), around 90% women of India had institutional delivery of which 70% took place in public health facilities. There is huge inter-state variation where 83.2% in Chandigarh but 53.9% women in Punjab delivered in public institutions. In Karnataka the figure was 64.8%. However, at the time of data collection, Ayushman Bharat - Pradhan Mantri Jan Arogya Yojana (AB-PMJAY) and Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA) were in the initial phase of being rolling out, hence these may be an underestimation of the current scenario<sup>5-6</sup>. Further, it was also reported in NFHS-5 (2019-21) that, 70.0% of pregnant women registered within first trimester, 58.1% had at least four ANC visits, whereas 44.1% consumed iron and folic acid for 100 days<sup>3</sup>. All of these figures were improved compared to those of NFHS-4 (2015-16). As per NFHS-4, 53.5% ANC were provided by public sector only, while 28.4% took place in private facilities<sup>4</sup>. Ultrasonography was done in 61.4% pregnant women,

although more proportion of women from higher wealth quintiles had ultrasound tests<sup>4</sup>.

The government of India launched the National Rural Health Mission (NRHM) in 2005, which was expanded into the National Health Mission (NHM) in 2013, after incorporating National Urban Health Mission (NUHM). Various maternal and child health related schemes and services are being operationalized under the umbrella of NHM. Some noteworthy strategies adopted under NHM to improve maternal health care to address the inequity of essential obstetric care including antenatal care (ANC) are as follows:

**Pradhan Mantri Surakshit Matritva Abhiyan (PMSMA):<sup>6</sup>**

Under PMSMA, which was launched in June, 2016; all pregnant women in the country are provided on a fixed day, free of cost assured and quality Antenatal Care and to screen high risk pregnancies by specialists/physicians. It also envisaged for delivering a minimum package of antenatal care services (including investigations and drugs) would be provided to the beneficiaries on the 9th day of every month at identified public health facilities (PHCs/ CHCs, DHs/ urban health facilities etc.) in both urban and rural areas in addition to the routine ANC at the health facility/ outreach. Health care providers from private sector are also engaged as volunteers to provide specialist care in Government facilities. Under this scheme, one Ultrasound (US) scan during the 2nd/ 3rd trimester of pregnancy along with other related laboratory investigation are recommended for all pregnant women.

**Janani Shishu Suraksha Karyakram (JSSK):<sup>7</sup>**

Provision was made under *Janani Shishu Suraksha Karyakram* for availability of ultrasound scan and other laboratory tests which were not available at a public health facility; in a public-private partnership mode and related expenditures are covered by the Government.

**Surakshit Matritva Aashwasan (SUMAN):<sup>7-8</sup>**

A newer initiative namely-SUMAN-Surakshit Matritva Aashwasan", launched on 10<sup>th</sup> October, 2019 aims to provide assured, free-of-cost and quality healthcare with dignity and respect towards the beneficiary and to obliterate denial of services for every woman and newborn visiting the public health facility aggregating existing services like JSSK, PMSMA etc. It envisaged to end all preventable Maternal and newborn deaths.

**State of the art Maternal and Child Health Wings (MCH wings):<sup>7</sup>**

MCH wings have been sanctioned at District Hospitals/District Women's Hospitals and other high case load facilities at Sub-District level, as integrated facilities for providing quality obstetric and neonatal care.

**Village Health, Sanitation and Nutrition Days (VHSND):<sup>7</sup>**

The VHSND is an outreach activity aimed at providing of maternal and child care including nutrition in convergence with the Integrated Child Development Services (ICDS) near the residences of the beneficiaries.

**Maternal and Child Health Card (MCPC):<sup>7</sup>**

The MCP Card is being used by all States as a tool for monitoring and improving the quality of MCH and Nutrition interventions.

**Web-enabled Mother and Child Tracking System (MCTS):<sup>7</sup>**

This is being implemented to help the health workers in planning for service delivery and identification of beneficiary due for Antenatal Check-up (ANC), Postnatal check-up (PNC) and Immunization services. It helps in identification of high-risk pregnant women and tracking of health conditions and assistance during the delivery of pregnant women.

**Leveraging the Network of ASHAs:<sup>7</sup>**

Accredited Social Health Activists (ASHAs) have been engaged to facilitate access to health care services by the community, particularly pregnant women<sup>5</sup>.

Within the purview of national health programmes, there are initiatives that widen the choice of a pregnant woman to select a private facility under certain circumstances. However, whether and to what extent such schemes contributed to increase the utilisation of private facilities for ANC is not well documented.

**Differential Utilization and the Issue of Quality of Care :**

Although, WHO has identified key parameters for quality ANC in 2016 under sub-domain of nutritional intervention, maternal and fetal assessment, preventive measures, intervention for common physiological symptoms and health system intervention for quality of care, the comprehensive assessment of quality of ANC has not been reported so far<sup>1</sup>. Basic services (iron and folic acid supplementation, tetanus immunization etc) and clinical (registration before weeks, at least four ANC visits, assessment of blood pressure, edema, anemia, weight, height and abdominal examination including fetal heart sound etc) parameters were used so far in Indian studies to assess the quality of ANC<sup>9-12</sup>. In such a study based on data collected in NFHS-2015-16, it was noted that around half of the Indian pregnant women received all components of care. However, there is gross variation across the states as well as social gradient<sup>9</sup>.

A review of 85 studies conducted across the globe could not synthesize clear demarcation between quality of ANC between public and private providers. They concluded that women selected care from such providers or settings where they found it is a positive experience fitting with their beliefs and values, was easy for them to access, affordable, and showed respectful behaviour<sup>13</sup>.

The World Health Organization (WHO) recommended one Ultrasound (US) scan before 24 weeks gestation to estimate Gestational Age (GA), improve detection of foetal anomalies and multiple pregnancies, reduce induction of labour for post-term pregnancy, and improve a woman's pregnancy experience<sup>1</sup>. If an early US scan was not performed, then stakeholders may consider performing a scan later in pregnancy to identify the



number of fetuses, fetal presentation, and placental location. However, this may not be available in each tier of public health facilities. Availability of ultrasound scan may be one reason to attract pregnant women to avail private facility for ANC. The JSSK and PMSMA broadened the opportunity to avail high end tests from accredited private institutions<sup>7</sup>. A positive association between health insurance coverage and full ANC utilisation has been found in a study based on the data of NFHS-4<sup>9</sup>. Only 20% women were covered by health insurance or health schemes and majority of these were beneficiaries of central or state government health insurance schemes<sup>9</sup>. Majority of the private insurance as well as the recently launched National Health Protection Scheme under the aegis of 'Ayushman Bharat' (AB-PMJAY) do not cover ANC services<sup>5</sup>. A study conducted in Karnataka reported that incentives by the Government facilitated the utilisation of public health facilities whereas lack of general cleanliness and poor infrastructure at public facilities were regarded as barriers<sup>10</sup>. Furthermore, factors such as accessibility, waiting time, unacceptability of providers were also reported as the reasons behind poor utilisation of ANC services<sup>11</sup>. Health professionals found to be spending more time in consultation in private facilities than public, which may be considered favorable for private facilities<sup>12</sup>. It was also reiterated in another study where the authors concluded that the dominant utilization of private sector services by richer households signify possible variations in quality of care and health care services between public and private sectors, including better infection control practices<sup>14</sup>. In addition, public health facilities may not be well-equipped with Emergency Obstetric Care (EMOC) management and may not be able to provide C-section birth services on a need-basis<sup>14</sup>. On the contrary, an assessment of 201 private sector healthcare facilities in Maharashtra, Jharkhand, and Uttar Pradesh based on 16 item checklist developed by FOGSI for Manyata programme, which mainly encompasses intra-partum care and immediate newborn care, including infection control; revealed that overall quality of maternity care in private healthcare facilities is poor, especially for clinical standards related to management of complications of labour<sup>15</sup>. Delivery load was a significant determinant of quality of care<sup>15</sup>.

Overall, a detailed account of the differences in antenatal care utilisations across all types of service providers as well as its loco-regional variation needs to be further explored. Without such evidence it is too early to comment, as a generalized note, on whether really women prefer to avail private facility over public ones.

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## Original Article

# Factors Influencing Non-utilization of Antenatal Care Services from Government Sector among Rural Pregnant Women — A Hospital-based, Cross-sectional Study in Vijayapura District of North Karnataka

Praveen S Ganganahalli<sup>1</sup>, Chandra Bhanu Singh<sup>2</sup>

**Background :** Pregnancy is one of the most important events in the life of Indian women. Maternal care includes care, during pregnancy and should begin from the early stages of pregnancy. Maternal mortality and morbidity remain high even though National Programs exist for improving Maternal and Child Health in India. Among several factors related to it one is less or non-utilization of free maternal healthcare services, especially amongst rural women.

**Objectives :** To measure the utilization of free Maternal Healthcare services & to study the factors determining the utilization of free Maternal Healthcare services by Rural Women during pregnancy.

**Methods :** The study was conducted on the women admitted in postnatal ward after delivery, by using structured proforma containing questionnaire which included socio-demographic variables, details of present pregnancy, delivery & details of utilization and non-utilization of Antenatal Care Services given by their local Government Health Facility. Also, questions were asked about the reasons regarding their preference to the Private Hospital for delivery in spite of free delivery service at Government Hospitals.

**Results :** The early identification of risk factors during pregnancy will be possible by Ultrasonography and other investigations, which is the main reason for a greater number of visits to private hospitals during pregnancy compared to Government Health Facility.

**Conclusion :** Strengthening of Government Health Facility in terms of specialist Manpower and Material like Laboratory/Equipment's/Drugs to handle the complications effectively during pregnancy or delivery by the specialist is need of the hour.

[J Indian Med Assoc 2022; 120(3): 12-5]

**Key words :** Pregnancy, Free, Services, Utilization.

Pregnancy is one of the most important events in the life of Indian women. Maternal care includes care during pregnancy and should begin from the early stages of pregnancy. Women can access Antenatal Care Services either by visiting a Health Center where such services are available or from Health Workers during their domiciliary visits<sup>1</sup>.

Promotion of Maternal and Child Health has been one of the most important components of the Family Welfare Programme of the Government of India and the National Population Policy 2000<sup>2</sup>.

According to the Guidelines from the Government of India, a minimum of four ANC's including early registration and first ANC in the first trimester along with physical examinations and abdominal examinations, investigation like Haemoglobin (Hb) estimation and Urine Routine, two doses of Tetanus Toxoid (TT) immunization and consumption of iron Folic

### Editor's Comment :

- Strengthening of Government Health Facilities in terms of specialists like Obstetrician, Anaesthetist, Neonatologist, Radiology expert and Material like Laboratory, Equipment, Drugs to handle the complications effectively during pregnancy or delivery.

Acid (IFA) tablets (6 months during ANC and PNC) are required<sup>3</sup>.

Maternal mortality rate is only 9/lakh live birth in UK as compared to 167/lakh live births in India, where as in Karnataka it is 133/1000 live births. Maternal mortality and morbidity remain high even though National Programs exist for improving Maternal and Child Health in India<sup>1</sup>. Among several factors related to it one is less or non-utilization of Free Maternal Healthcare Services, especially amongst Rural & Urban Slum population due to lack of awareness or access to Healthcare Services<sup>1,4</sup>.

So the study was planned to measure the utilization of free Maternal Healthcare services and also to find the factors determining the utilization of free Maternal Healthcare Services by Rural Women during Pregnancy.

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**MATERIAL AND METHODS**

A Cross sectional study was conducted in the Obstetric Ward in the month of July & August, 2019 on women delivered in Present Teaching Hospital. Women belongs to Rural Area were included in the study whereas women from Urban Area or belonging to Rural Area but residing in Urban/Semi-Urban area were excluded from the study.

By considering the admission of Rural Pregnant Women for delivery to the present Teaching Hospital 50% among all, the sample size calculated was 100 by using the formula  $n=4pq/E^2$  whereas  $n$ =sample size,  $p$ =prevalence of Rural women admission to the hospital,  $q$ =no admission of Rural women to the hospital,  $E$ -allowable error of 10.

Sampling Method: The study was carried out by using structured proforma containing questionnaire. The women admitted in postnatal ward after delivery were interviewed after taking informed consent by using the proforma which included Socio-Demographic variables, details of present pregnancy, delivery & details of utilization and non-utilization Antenatal care services given by the Government Health Facility. Few questions were asked to find out the reasons regarding their preference to the Private hospital for delivery in spite of free delivery service at Government hospitals. The information's collected were entered in their respective proforma.

The study was started after taking clearance from Institutional Ethical Committee and permission from Head of the department of Obstetrics & Gynaecology. Data collected was entered in Excel sheet and analyzed for frequency distribution of variables. Association between variables was seen by applying tests of significance. P value less than 0.05 was considered statistically significant. Data was analyzed using SPSS v.17.

**RESULTS**

Total 112 Rural women delivered in present Teaching Hospital were interviewed during the study period of two months.

According to Table 1, 88% of the participants were educated (45% below & 55% above college level), 37% belonging to lower class (IV & V) according to modified B G Prasad classification and 88% were Housewives. Mean age of women was  $24\pm 3.9$  years with minimum age 19 years & maximum 37 years among all the participants.

According to Fig I, about 44% of the participants were Primiparas followed by 38% with Parity-2 where as women with Parity-3 & above (18%) were few among all.

Education status		Socio-Economic Status		Occupation	
Variable	No (%)	Variable	No (%)	Variable	No (%)
Illiterate	15 (13)	Class I	05 (4)	Housewife	98 (88)
Primary school	18 (16)	Class II	10 (9)	Labour	06 (5)
Higher school	32 (29)	Class III	56 (50)	Tailor	03 (3)
College	11 (10)	Class IV	28 (25)	Teacher	05 (4)
Graduate	32 (29)	Class V	13 (12)		
Postgraduate	04 (3)				
Total	112(100%)	Total	112 (100%)	Total	112 (100%)

Among all the participants 70% of them told that Primary Health Center is located in their village whereas only 30% women belongs to the village having Sub centers. Average distance which was travelled by the participants to reach Primary Health Center was  $4.13\pm 4.08$  km with minimum distance of 1km to maximum 15km to avail the services.

About 97% of the participants did registration of their pregnancy at Primary Health center catering their village where as only 3% had not registered. The reason mentioned for not registering was that the Mothers House is in the place where the present institute is located and they had plan to deliver baby in private hospital.

Among the participants 58% informed that the health workers visited their home during pregnancy to give advices regarding Ante Natal Care (ANC), Delivery and Nutrition Supplementation whereas 42% had no home visit by the Health Workers of their area Health Centre. About 57% of the participants had Mother Health Card regarding the service utilization of ANC from the Primary health center whereas 43% not having or not received Mother Health Card.

On interview regarding the important ANC are service to be taken during pregnancy showed following observations, among all 90% had taken two doses of Tetanus Toxoid (TT) injection followed by 10% with either one or three doses of TT. Out of total participants 52% had taken TT injection at Private specialist hospitals (during confirmation of pregnancy by USG) whereas 48% in Government Health Centres.

About 55% have purchased the IFA tablets from private medical shops (prescribed by Private

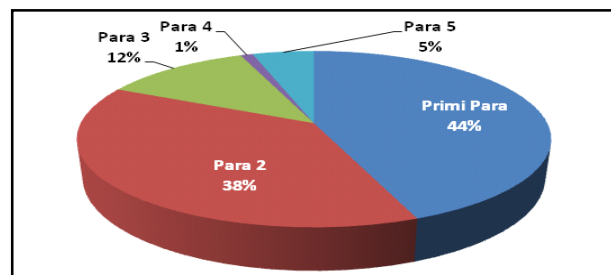


Fig 1 — Percentage Distribution of Participants According to Parity

Practitioners) whereas 45% taken from the Government Health Facilities (low purchasing capacity of participants).

About 95% had underwent Ultrasound scanning for their pregnancy at Private Scanning Centers due to non availability of scanning service at Government set up whereas only 5% had undergone scanning at Government Setups. Majority of the participants had undergone Ultrasound scanning 3 to 4 times (69%) whereas 22% had undergone about 2 times followed by 3% only 1 time during their entire pregnancy.

About 97% of the participants were visited Private Obstetrician's Hospital for ANC services, like routine ANC Checkup, Investigations, Ultrasound scanning or for taking treatment for complications. Among all only 3% had never visited the Private Hospital for ANC Services.

The main reason for Private Hospital visit was Ultrasound scanning (97%) followed by routine ANC checkup (88%) from the specialist (Obstetricians) whereas other reasons were routine Investigations related to pregnancy (78%) & to take treatment for pregnancy related complications like Pregnancy induced Hypertension, Gestational Diabetes, Pre-eclampsia, Oligohydramnios etc.

Among all the participants of the study around 37% were not planned to deliver in Government Health setup on beforehand only whereas remaining 63% were either referred here by Government Doctors for complications during delivery or changed their mind to Private Setup Delivery.

According to the figure II, the most common reason to undergo delivery in Private Teaching Hospital found was the complication (60%) due to pregnancy and delivery including twins (one case). Lack of facility, Poor service & non availability of specialist doctors to handle complications (17%) were the reasons for not delivering in Government Set up. Around 23% delivered in Private hospital due to family pressure, family member working in the hospital or mothers native place was near to it.

Fig 3 shows, comparison between number of visits among Government Health Centers & Private hospitals of Obstetric specialty during pregnancy according to which there was decreasing trend seen with increase in number of visits in Government Health Centers compared to Private hospitals where there was increasing trend observed with increase in number of visits. This difference in trends was found statistically significant ( $\chi^2=63.49, p<0.0001$ ).

Most important reason for low utilization of services during pregnancy and delivery at Government Healthcare set ups was complications arising due to pregnancy/delivery and no specialists care service

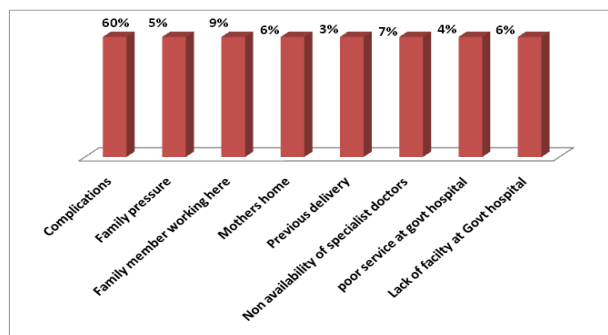


Fig 2 — Percentage Distribution of Reasons for Delivery at Private Teaching Hospital

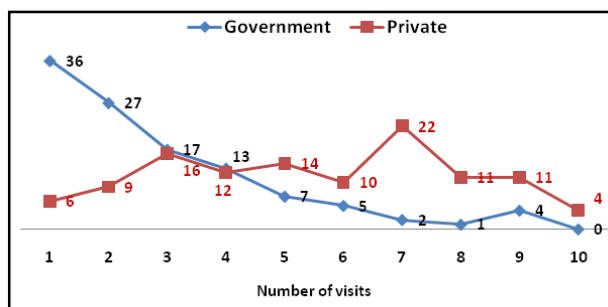


Fig 3 — Comparison of Number Visits by Participants in Govt & Private Health Facility

available to handle it to save mother and baby as shown in Table 2.

### DISCUSSION

Among the women delivered included in study majority (88%) are educated, 2/3<sup>rd</sup> belongs to middle & upper class and 88% are Housewives. About 70% of participants are staying in village containing Primary Health centers where Normal Delivery Services are available. Maximum distance to be traveled is 15 kms from their village to avail Antenatal care services from PHC.

Mumtaz S *et al*<sup>6</sup>, studied status and determinants of Maternal Healthcare utilization in Afghanistan according to them overall 17.8% of women attended four or more ANC visits, about 53.6% utilized a Skilled Birth Attendant and 3.4% of women gave birth through Cesarean Section. Women's Education, Wealth Status, Autonomy, Urbanity and availability of their own transport were found to be the major determinants of service utilization.

Deepak C *et al*<sup>6</sup> re-emphasized that utilization of maternal Healthcare services is affected by Multiple Socio-demographic Factors like maternal education, religion and parity of women. Education increases awareness about health, availability and accessibility of services which help develop the confidence.

Lalit KR *et al*<sup>7</sup> studied the utilization of ANC, Institutional delivery and PNC was 59%, 28% and 26% respectively. There was also a large significant variation



Table 2 — Factors Affected for Utilization of Maternal Health Services by Participants at Government Health Facility

Services provided by Government health facility	Utilization rate	Factors affected
Registration at Primary Health Center	97%	Local PHC/SC available
Health workers visit to home during pregnancy	58%	Visiting private hospital for care during pregnancy
Mother card for service utilization of ANC care	57%	Visiting private hospital for care during pregnancy
TT injection	48%	TT injection taken in private hospital during visit
IFA tablets	45%	Belief of poor-quality drugs supplied free of cost
Ultrasound scanning	05%	No scanning service available
Delivery at Government hospital	00%	No specialist doctor available to handle complications due to pregnancy & during delivery

in utilization of services of ANC and delivery in between Rural and Urban settings. Households' Socio-economic status, Mother's education, Religion and Birth order was the most-important determinants associated with the use of any ANC and institutional delivery.

Among those who visited private hospital, the most common reason is for Ultrasound scanning (97%) followed by routine investigations (78%) & ANC checkup (68%). About 36% of the women visited Private Hospital for complications occurred due to pregnancy like Pregnancy Induced Hypertension, Gestational Diabetes, Oligohydramnios, Pre-eclampsia etc.

Singh R *et al*<sup>8</sup> found in their study, 83 % of women had ANC of them, 61% reported three or more ANC visits. Although 68% of women delivered in a health facility, 29% stayed for at least 48 hours. In the adjusted analysis, women with increasing number of contacts with the health worker during the period of pregnancy, exposed to mass-media were more likely to have at least three ANC visits during pregnancy.

In Rushender *et al*<sup>9</sup> study 60.2% of selected households are located beyond 5kms. 85.5% of respondents were aware of the PHC. 71.2% of respondents had satisfactory opinion about the Health Services. 81.65% of the ANC mothers had utilized the PHC, 77.98% for TT immunization, 75.24% for delivery, 75.76% for Postnatal Care and 79% for Immunizing their children.

Chauhan BG *et al*<sup>10</sup>, findings show use of Maternal Healthcare services in India higher among women of Urban area than Rural area. Lower utilization by Rural population may be due to several barriers like cost of transportation, cost of care and low awareness about health-promoting behavior.

## CONCLUSION

The early identification of risk factors during pregnancy will be possible by Ultrasonography and other investigations, which is the main reason for more number of visits to Private Hospitals during pregnancy compared to government Health Facility. The most important reason for opting Private Hospital for delivery by pregnant women herself or by family is non availability of specialist doctors or facility to handle complications due to pregnancy or delivery in the Government Health Facility.

Strengthening of Government Health Facility in terms of specialist Manpower like Obstetrician, Anesthetist, Neonatologist, Radiology expert and Material like Laboratory/Equipment's/Drugs to handle the complications effectively during pregnancy or delivery by the specialist.

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## Original Article

# In Hospital Mortality in Patients with Impaired Fasting Glucose and Acute Myocardial Infarction in a Tertiary Care Centre of Rural Bengal

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**Introduction :** The Cardiovascular mortality in Diabetics is 2-4 times higher than in Non-diabetic population. But there is still controversy regarding Pre-diabetes (IFG and IGT) as a Cardiovascular Risk Factor.

**Aims and Objectives :** In this study we aimed to investigate the early in-hospital mortality among Acute Myocardial Infarction (AMI) patients having Impaired Fasting Glucose (IFG) during the first 7 days of hospitalization.

**Materials and Methods:** A total of 150 AMI patients were evaluated and followed up for their glycemc status and early in hospital mortality (first 7 days) at Burdwan Medical College, Burdwan, West Bengal.

**Result and Analysis:** Mortality in patients having IFG (18%) was higher and as much as in DM (20%) compared to euglycemic (4%) patients but the mortality is not correlated with mean Fasting Plasma Glucose (FPG) level.

**Conclusion :** IFG (ie, pre-diabetes) increases Cardiovascular mortality as much as diabetes. So, IFG may be a marker or risk factor for mortality but lowering FPG in AMI patients is unlikely to yield beneficial effect regarding mortality.

[J Indian Med Assoc 2022; 120(3): 16-8]

**Key words :** Impaired Fasting Glucose (IFG), Pre-diabetes, Diabetes Mellitus (DM), Acute Myocardial Infarction (AMI), Fasting Plasma Glucose (FPG)

**D**iabetes Mellitus is an important Cardiovascular Risk Factor. The Cardiovascular mortality in Diabetic Patients is 2-4 times higher than in non-diabetic population<sup>1</sup>. In diabetics, 70-80% of deaths occur because of Cardiovascular Diseases. Pre-diabetes (IGT and IFG) now believed to be as risk factors for Diabetes and Cardiovascular Disease Development<sup>2</sup>. Though less severe than diabetic patients, growing evidence suggests that Pre-diabetic patients have a substantially increased risk of Cardiovascular disease and death compared with normal patients. Observations also indicate that early identification and management of individuals with Pre-Diabetes have the potential to reduce the incidence of Diabetes and its related complications.

### Editor's Comment :

- The Cardiovascular mortality in diabetic patients is 2-4 times higher than in non-diabetic population. But there is still controversy regarding pre-diabetes (IFG and IGT) as a Cardiovascular risk factor. We found out that IFG may be a marker or risk factor for mortality but lowering FPG in AMI patients is unlikely to yield beneficial effect in respect of mortality.

### MATERIALS AND METHODS

#### Study Subjects :

In a Tertiary Care Hospital based cross sectional study of Eastern Part of Rural India, we aimed to investigate the mortality rate among AMI patients during the first 7 days of hospitalization. A total of 150 AMI patients admitted to our Coronary Intensive Care Unit were included and according to their glycemc status they have been grouped into - (1) The patients with diabetes (FPG  $\geq$ 126 mg/dl),

(2) Patients with IFG (FPG between 100-125 mg/dl) and (3) Euglycemic (FPG <100 mg/dl) patients; and followed up.

Patients with other Non-cardiac Acute Illnesses, associated infections and other associated chronic major illnesses like Stroke, COPD, Bronchial Asthma, Chronic Liver Disease; Chronic Kidney Diseases etc. which could affect the mortality outcome had been excluded from this study.

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**Biochemical Tests :**

Venous blood was taken in the morning after an overnight fast for at least 12 hours for biochemical analysis. Plasma Glucose was measured by Standard Laboratory Based Glucose Oxidase method. Diabetes was diagnosed according to “American Diabetes Association” when a previous or current 12 hours fasting Glucose level is 7mmol/l or greater ( $\geq 126\text{mg}\%$ ). Other measurements were done by standard routine laboratory methods.

**Statistical Analysis :**

The SPSS for the Windows 20.0 statistical package program has been used for data analysis. The quantitative data of the groups were compared using ANOVA (ANalysis Of VAriance) and Tukey’s HSD post hoc test for multiple comparison and the qualitative data were compared using Chi-square tests. P value < 0.05 was considered significant. The study has been approved by Local Ethical Committee of our hospital.

**RESULTS**

In our study 84.7% were male and 15.3% were female. The groups were age and sex matched. The mean BMI was higher in diabetics compared to euglycemic and patients with IFG. All females were non-smoker and 38.5% males were smoker with no significant intergroup difference. 44.7% patients were hypertensive in our study. Though 56% of Diabetics were Hypertensive, the intergroup differences were not significant. Both the mean Systolic (SBP) and Diastolic Blood Pressures (DBP) were significantly higher in diabetic patients. The mean Serum Cholesterol and HDL levels were similar in three groups; and the mean Triglyceride and LDL levels were significantly higher in Diabetic patients, but only the higher mean Triglyceride level was significantly associated with early in-hospital mortality (Table 1).

It was found in our study that the mortality was 4% in Non-diabetic group, 20% in diabetic group and 18% in patients with Impaired Fasting Glucose (IFG). Mortality in patients having IFG and DM were significantly higher compared to Euglycemic patients (p value 0.025 and 0.014). However, it was similar between patients with IFG and Diabetic patients (p value 0.799).

Female mortality (26.1%) was higher than male mortality (11.8%), though not

significant statistically. Mortality in this study population was significantly related with IFG, DM, serum Triglyceride and BMI (Table 2).

The mean Fasting Plasma Glucose (FPG) level was not correlated with mortality. The mean serum Triglyceride level was positively correlated with mortality.

**DISCUSSION**

The early in-hospital mortality in AMI patients were approximately the same in patients with IFG and Diabetes and this was significantly higher compared to the individuals with Normal Glucose Levels.

The mortality was also higher in those with increased Serum Triglyceride Level and increased BMI which are common associates of DM.

But in our study population, the mortality was not significantly correlated with FPG level; it was only positively correlated with increased Triglyceride level.

M. Hanefeld *et al*<sup>2</sup> demonstrated in their study that the male sex, higher mean age, high blood pressure, increased serum Triglycerides, increased postprandial Blood Glucose and smoking as independent risk factors for death in Myocardial Infarction.

Haffner SM *et al*<sup>3</sup> and Wheathcoft SB *et al*<sup>4</sup> also demonstrated that the Cardiovascular risk increases in the pre-diabetic period. Detecting patients in this stage and protecting them against the harmful effects

Table 1 — Baseline characteristics and outcome of the patients

Parameters	Non-DM group	IFG group	DM group	Sig
Age(in years)	52.9±6.6	54.7±5.8	54.1±5.6	0.307
Male	84%	86%	84%	0.950
BMI(kg/m <sup>2</sup> )	27.3±2.5	26.8±2.1	29.3±2.6	0.001
Smoker (%)	36%	30%	32%	0.809
Hypertensive (%)	38%	4%	56%	0.140
SBP(mm of Hg)	114.7±14.5	117.4±10.1	134±15.2	0.001
DBP(mm of Hg)	77.8±8.1	77.3±6.4	88.6±11.1	0.001
Cholesterol (mg/dl)	203.3±27.7	199.1±26	200.5±23.6	0.716
Triglyceride (mg/dl)	181.7±27.6	198.9±30.6	225.9±32.0	0.001
LDL(mg/dl)	129.0±20.5	126.9±17.5	144.7±14.8	0.001
HDL(mg/dl)	41.8±3.4	41.7±3.1	42±3.4	0.851
Fasting plasma glucose(mg/dl)	87.6±7.3	114.4±7	193.6±29.1	0.001
Complication developed(%)	28%	44%	44%	0.165
Mortality(%)	4%	18%	20%	0.043

Table 2 — Simple Linear Regression analysis

Unstandardized Coefficients	Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B
B	Std. Error	Beta		Lower Bound Upper Bound
(Constant)	0.744	0.735	1.013	0.313 -0.709 2.197
FPG	-0.001	0.002	-0.088	-0.383 0.702 -0.004 0.003
TG	0.002	0.001	0.206	2.152 0.033 0.000 0.004

a. Dependent Variable: outcome regarding mortality during early in-hospital period

of insulin resistance helps to prevent Coronary Heart Disease.

Mehmet Uçucu, *et al*,<sup>5</sup> also demonstrated that the IFG affects mortality as much as diabetes. Fasting Plasma Glucose is helpful, in determining the cardiovascular risks and in the modification of the therapy to reduce the risk of CHD.

In Diabetics, Coronary Artery Atherosclerosis is aggressive and has an early onset<sup>6</sup>. It is thought that in the pathogenesis of diabetes, long before overt Hyperglycemia occurs and diabetes is diagnosed, there is a long period of insulin resistance, when the blood Glucose is maintained at normal levels by compensatory Hyperinsulinemia.

It was demonstrated that Cardiovascular risk increases also in this Pre-diabetic Period<sup>7,8</sup>.

Recent report from the Rancho Bernardo Study also indicated that pre-diabetic subjects have increased cardiovascular Risk Factors prior to the onset of Clinical Diabetes<sup>9</sup>.

Events associated with Atherosclerosis start to develop long before the stages when this can be detected as IFG and IGT<sup>10</sup>. Detecting patients in this stage and protecting them against the harmful effects of insulin resistance helps to Prevent Coronary Heart Disease.

### CONCLUSION

In conclusion, the IFG (ie, pre-diabetes) increases cardiovascular mortality as much as diabetes. So, the IFG may be a marker or risk factor for mortality but lowering FPG in AMI patients is unlikely to yield

beneficial effect as per this study. Controlling obesity (lowering BMI), lowering Serum Triglyceride Level and treating IFG in the general population may improve the outcome of AMI patients.

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— Hony Editor

## Original Article

# A Retrospective Analysis of Disease-free Survival of 2332 Cases of Cancer of the Oral Tongue from a Single Institute in Eastern India from 1998-2017

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**Background :** Over half the patients of Oral Tongue Cancers in India present with locally advanced disease and Nodal Metastasis. Additionally many of them avoid surgical intervention due to fear or belief that Cancer is a Death Sentence.

**Materials and Methods :** A Retrospective analysis of all Oral Tongue Cancer patients treated at Mahavir Cancer Sansthan from 1998 to 2017 was done. The primary aim was to find the Disease Free Survival (DFS) rates of these patients. The secondary aim was to examine if surgical excision improved DFS rates.

**Results :** The mean DFS for all stages was 51 months varying from 90 months in stage 1 to 30 months in stage 4. One in every three patients survived without recurrence of disease for more than five years. The addition of surgical excision at any stage of Cancer, when possible, resulted in a significant increase in DFS.

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**Key words :** Oral Tongue Cancer, Disease-free Survival, Surgery, Retrospective.

Majority of patients of Oral Tongue Cancer in India present in stages three and four<sup>1</sup> leading to reduced disease free survival rates<sup>2-4</sup>.

The ICMR Consensus Document for Management of Tongue Cancer<sup>5</sup> recommends single modality treatment for early stage Cancers and Multimodality therapy for advanced stage disease but Surgery with or without an Adjuvant Therapy is the preferred modality. Retrospective studies and randomized trials have found significantly reduced survival rates for patients treated without surgery<sup>6,7</sup>. But very often patients in India are treated by Radiotherapy either due to their choice, comorbidities or locally advanced disease that make them unsuitable for Surgery<sup>4</sup>.

Mahavir Cancer Sansthan was established in Patna in 1998 as a Tertiary Cancer Therapy Centre. Initially it housed a Cobalt Teletherapy Machine and all patients were treated by Radiotherapy. Gradually other branches of therapy were established and Multimodality Therapy became the norm for most patients of Oral Tongue Cancers. The institute attracts

### Editor's Comment :

- Average Disease free survival of patients of Oral Tongue treated at Mahavir Cancer Sansthan is 51 month and varies from 90 months for stage 1 to 30 months for stage 2.
- Surgical excision of tumour should be done whenever possible.

patients from Bihar, Jharkhand, North Bengal, Parts of Nepal and Bangladesh. It has catered to over two Lakh Cancer patients during its years of service.

The Authors did a Retrospective Analysis of Oral Tongue Cancer patients treated at Mahavir Cancer Sansthan between 1998-2017 to answer two questions: what is the disease free survival of tongue cancer patients in Eastern India and does the addition of Surgery, when possible, increase disease free survival.

### MATERIALS AND METHODS

This study was approved the ICE-RMRIMS Ethics Committee.

The treatment records of all Biopsy proven patients of Oral Tongue Squamous Cell Cancers (SCC) (ICD sites C02.0-C02.3 excluding C01, C02.4, C02.8 and C02.9)<sup>8</sup> were accessed and relevant data extracted. All patients who had Palliative Therapy, treatment outside the institute, incomplete therapy or incomplete follow up, incomplete treatment records or patients with histology other than SCC were excluded.

Variables examined included age, gender, WHO grade of differentiation<sup>9</sup>, TNM and Clinical stage as per AJCC 7<sup>th</sup> edition<sup>10</sup>, type of definitive therapy, outcome of therapy and whether any salvage therapy

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was proposed or used. The type of definitive therapy was classified into 'surgical' if it included Surgery, surgery with Radiotherapy(RT)/ Chemoradiotherapy (CRT) or Neoadjuvant Chemotherapy (NACT) with surgery with RT/CRT; and 'Non-surgical' if it included RT, CRT, NACT with CRT, Brachytherapy with RT/CRT or Brachytherapy. All Doses of Radiotherapy/ Brachytherapy were converted to Equivalent Total Dose of 2 Gy fractions using the Linear Quadratic Equation<sup>11</sup>.

Outcome of therapy was divided into 'Failure' if the patient experienced recurrence of Malignant Disease or 'Censored' if no failure was experienced or patient expired before recurrence. If there were Cytological, Histological or Radiological reports giving proof of recurrence these were noted as the method of diagnosis, otherwise the method of diagnosis was classified as 'Clinical'. The site of recurrence was classified as – 'Local' if it occurred within the oral cavity; 'Regional' if it occurred within the draining nodal basin; and 'Distant' if it occurred in distant organs.

'Disease Free Survival (DFS)' was defined as the period from commencement of definitive therapy to first recurrence or last date of follow-up, whichever was earlier. 'Updated DFS' was defined as the period from commencement of definitive therapy to the last telephonic update when the patient could be contacted. 'Diagnosis to Treatment Initiation Time (DTIT)' was defined as the period between first examination at the institute and commencement of definitive therapy. 'Treatment Package Time (TPT)' was defined as the period between commencement and end of Definitive therapy including any Adjuvant therapy. 'Days of default' was defined as any number of days of gap in therapy from first presentation to end of therapy of more than seven days, since seven days is the kick-off repopulation time for Head and Neck Cancers<sup>11</sup>.

If the patient was offered Salvage Surgery or re-irradiation he/she was considered salvageable; if the patient was offered Palliative Chemotherapy or best supportive care he/she was non-salvageable. If the records did not mention any Second Line Therapy, it was considered a missing value.

The data was stored in EXCEL spreadsheet and 'DAYS' function used to calculate the time intervals. DFS was converted into year-fractions using 'YEARFRAC' function and multiplied by twelve to obtain the same in months. Statistical analysis was done using SPSS version 20. Tests used included Chi-square, Mann-Whitney, ANOVA/Kruskal – Wallis, Kaplan-Meier and Cox Proportional Hazard. Probability levels less than 0.05 were considered significant.

## OBSERVATIONS

2332 biopsy-proven Oral Tongue Cancer patients were treated at Mahavir Cancer Sansthan between 1998 and 2017. In 1771 cases were excluded for the following reasons – 290 due to Palliative Therapy, 810 for refusing treatment, 460 for having undergone treatment at other institutes, 153 due to incomplete therapy, 18 because of Histologies other than Squamous Cell Cancer, 7 because they received less than 40 Gy Radiotherapy and 38 cases because they had zero days of follow-up. This left 561 analysable cases of Oral Tongue Cancer.

The Demographic and Clinical Characteristics and results of therapy are given in Table 1.

The median follow-up, estimated using the reverse KM method<sup>12</sup>, was found to be 18.7 months (95% CI: 16 – 21 months) and update median follow-up after telephonic contact was 26.6 months (95% CI: 20 – 33.2 months). The median DFS was 11 months (95% CI: 8 – 14 months), while updated DFS was 11.5 months (95% CI: 6 – 16.6 months). Hereon all survival analysis was done using updated DFS. Five-year DFS was 33.6%. 57.8% patients experienced recurrence within 24 months of therapy. 64% recurrences were local while 16% were nodal. Only 8% patients could be offered Salvage Therapy.

The results of univariable KM and multi-variable Cox Proportional Hazard analysis is given in Table 2. The clinical stage of disease, type of therapy (surgical *versus* non-surgical) and presence of default were found to significantly influence disease-free survival. Treatment Package Time tends to significance ( $p = 0.06$ ) and hence should be considered an important predictor.

Figs and the attached Table compares the survival curves for 'Surgical' versus 'Non-surgical' therapy stratified by clinical stage.

## DISCUSSION

The median follow-up of 19 months in our study is similar other Indian studies<sup>4,13</sup> but much less than the 36-45 months recorded by foreign authors<sup>14-16</sup>. Probably, this indicates the time after which an Indian patient will stop surveillance due to either poverty, logistic barriers or Lack of Awareness.

The overall five year DFS of 34% is also lower than the results of other Indian and Foreign Authors<sup>4,13-15</sup> but our series had a higher proportion of Stage 4A and 4B patients (44% *versus* 15-29%).

Surgical excision of the tumour was a very significant predictor of DFS at each stage of the disease. In Stages 1 and 3 the Surgery group did not

Variable	percent	P value
<b>Gender :</b>		
Male	417	74.3
Female	144	25.7
<b>Age (mean ±SD) :</b>		
Male	48 ±14	0.148
Female	49.6 ±11	
Median age * gender		
<b>Grade of Differentiation :</b>		
Well Differentiated	153	56
Moderately differentiated	107	39
Poorly differentiated	13	5
<b>Clinical T Stage :</b>		
T1	61	11
T2	189	35
T3	104	19
T4	191	35
<b>Clinical N Stage :</b>		
N0	279	51
N1	144	27
N2a	38	7
N2b	57	10
N2c	21	4
N3	5	1
<b>Clinical Stage :</b>		
1	53	9.7
2	168	30.8
3	86	15.8
4	239	43.8
Stage * Differentiation		0.119
<b>Type of therapy :</b>		
Surgery	32	5.7
Surgery + RT <sup>β</sup>	162	28.9
Surgery + CRT <sup>γ</sup>	72	12.8
NACT + Surgery + RT/CRT <sup>δ</sup>	20	3.6
Radiotherapy	113	20.1
Chemoradiotherapy	115	20.5
RT + Brachytherapy	29	5.2
NACT + RT/CRT	16	2.9
Brachytherapy	2	0.4
Therapy * Stage 1/2		0.088
Therapy * Stage 3/4 <sup>ε</sup>		0.03
<b>Outcome of therapy :</b>		
Failure due to recurrence	300	53.5
No recurrence	261	46.5
<b>Site of Recurrence :</b>		
Local	191	63.9
Regional(Nodal Basin)	47	15.7
Distant	24	8.0
Local + Regional	35	11.7
Others	2	0.6
<b>Method of diagnosis of recurrence :</b>		
Cytology :	60	20
Histopathology	44	15
Radiology	34	11.4
Clinical	159	53.2
Others	2	1
Diagnostic mode*type of therapy <sup>ν</sup>		<0.01
<b>Salvage Therapy :</b>		
Applicable	155	51
Not Applicable	25	8
Not Recorded	123	40.6
Salvage*Type of therapy		0.19

β - Radiotherapy, γ - Chemoradiotherapy, δ - Neoadjuvant Chemotherapy, ε - this difference can be explained by number T4b (inoperable patients) who were given RT/CRT, ν - clinically diagnosed recurrences were commoner among patients with non-surgical therapy

Variable	p value	
	univariable	multi-variable
Clinical Stage of disease	< 0.01	0.018
Default in treatment – yes/no	< 0.01	< 0.01
Type of therapy – surgical/non-surgical	< 0.01	< 0.01
Treatment Package Time(TPT)	0.284	0.06
Grade of differentiation	0.685	0.766
Age	NA	0.407
Gender	0.144	0.134
Clinical T stage	< 0.01	0.505
Clinical N Stage	< 0.01	0.617
Diagnosis – Treatment Initiation(DTI)	< 0.01	0.394

attain median survival on a maximum follow up 140 months. An equal proportion of early stage and late stage patients underwent surgical therapy (H = 2.322; p = 0.50) and Radiotherapy (H = 3.040; p = 0.37). Similar results have been recorded by other authors<sup>6,14,17,18</sup>. A randomized trial comparing Surgery and Radiotherapy versus Chemoradiotherapy found increased survival in the surgical arm which failed to reach statistical significance but it included Advanced Tongue Cancer patients only<sup>7</sup>. Therefore, we suggest that surgery should be a part of the therapeutic regime whenever possible.

The median 'Diagnosis to Treatment Initiation' time (DTI) and 'Treatment Package Time' were 28 days (Interquartile range: 16-51 days) and 62 days (Interquartile range: 47-76 days), respectively. A systematic review of both intervals found threshold values from 20-120 days and 77-100 days respectively<sup>19</sup>. Since the values in our series was within the threshold range and neither was found to affect survival.

Figures (1-5) — Survival Curves of Oral Tongue cancer patients stratified by clinical stage and type of therapy with

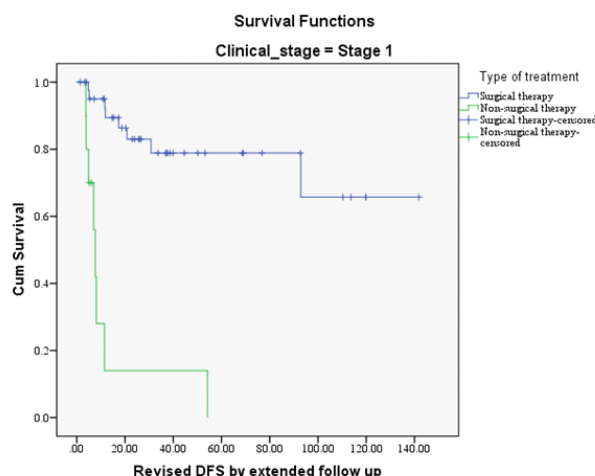


Fig 1

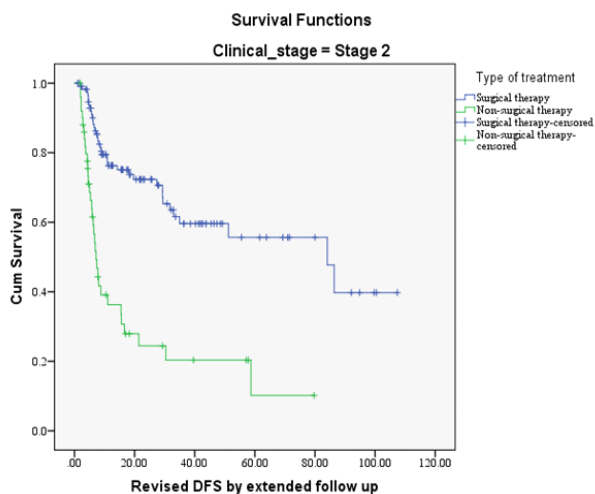


Fig 2

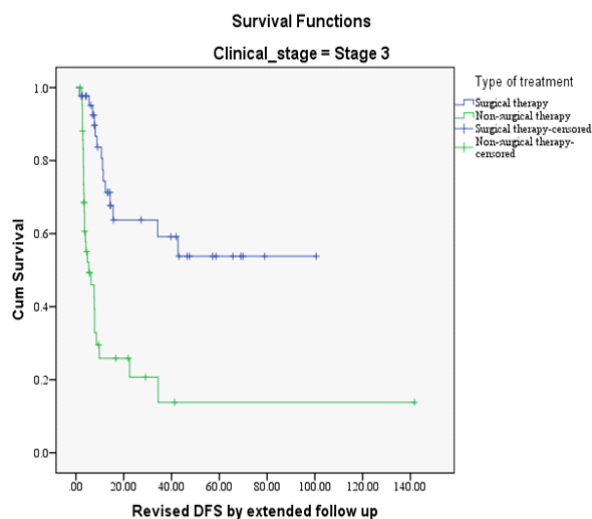


Fig 3

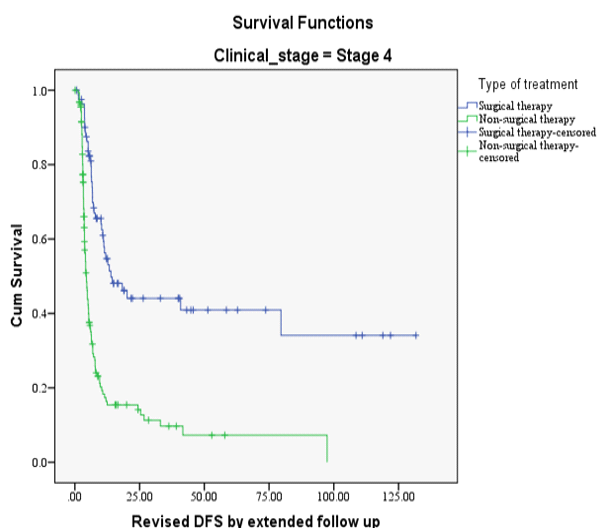


Fig 4

	Stage 1	Stage 2	Stage 3	Stage 4
Surgical Therapy	**	84.1	**	13.9
Non-surgical Therapy	7.7	7.2	5.4	4.5

\*\* - median DFS not reached at 140 months of follow-up

Fig 5

The mean duration of default was 9 days (95% CI: 5-15 days) and although only 7.3% patients defaulted it was a very significant independent predictor of the outcome. 83% defaults occurred during radiotherapy reducing the planned to administered EQD 2 by 10-60%.

All other predictors including age, gender, clinical T and N stages and grade of differentiation were not significant. While clinical T and N stages were found significant in univariable analysis they were insignificant

on multivariable analysis, probably because they get subsumed in the clinical stage.

**Limitations of the Study :**

This is a retrospective study done on hospital records accumulated over a 19 year period and therefore suffers from all the disadvantages of any such study<sup>20</sup>. Not all records were meticulously maintained and when found incomplete, such records had to be excluded. The authors have tried to eliminate sources of bias by strictly adhering to the inclusion and exclusion criteria and making all Radiotherapy regimes as comparable as possible.

There was no Cytological or Histological Proof of 52% of recurrent Tumours and this was commoner in patients undergoing non-surgical therapy ( $p < 0.01$ ). Probably, most of these patients were of advanced stage and when they failed either the clinician felt it unnecessary to pursue a Biopsy for just palliative Therapy or the patient refused biopsy/FNAC or financial constraints forced the patient to Abandon Therapy.

**Conclusions :**

- (1) The mean disease-free survival of a Tongue Cancer patient in Eastern India for all stages is 51.4 months, varying from 90 months in Stage 1 disease to 30 months in Stage 4 (mean DFS has been quoted since median DFS for stage 1 patients was not reached at the conclusion of this study).
- (2) One in three patients experience disease-free survival for five years or more.
- (3) 60% patients are likely to experience recurrence of Cancer within 24 months of Therapy.
- (4) The addition of surgical excision of the disease



makes a very significant difference in the outcome ( $p < 0.01$ ).

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**Conflict of Interest :** None

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## Original Article

# Pulmonary Hypertension in Hemoglobinopathies : A Neglected Entity

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**Background :** Hemoglobinopathies constitute a heterogeneous group of Hereditary Hemoglobin Disorders. Cardiovascular complications are among the leading causes of morbidity and mortality in Hemoglobinopathies. In the wide spectrum of Cardiovascular manifestations, Pulmonary Arterial Hypertension (PAH) holds a prominent place. Screening for Pulmonary Hypertension should be an essential component in assessment of patients with Hemoglobinopathies and may be accomplished by Transthoracic Doppler Echocardiography which is most established screening tool for Pulmonary Hypertension and is widely available and cost-effective.

**Objective :** This study aims to determine the presence of Pulmonary Hypertension in Hemoglobinopathies.

**Method :** Institution/Hospital based, Non-interventional, Observational Descriptive, Cross-sectional study conducted amongst 76 patients of Hemoglobinopathies (>12 years) in North Bengal Medical College and Hospital, Darjeeling. Detailed history and physical examination along with non invasive tests like ECG, Chest X-ray and Echocardiography were performed in all study population to detect PAH. Data was analysed using standard statistical method.

**Result :** 30.26% of patients with Hemoglobinopathy had PAH in Echocardiographic findings, of which 25% had mild and 5.26% cases had Moderate PAH. It was most prevalent in E- $\beta$  thalassemia, followed by Sickle  $\beta$  and  $\beta$  thalassemia major respectively. The clinical indicators associated with increased risk of PAH in Hemoglobinopathies were presence of Severe Anemia, transfusion >10 U/year, Iron overload state, Splenectomy and their combinations.

**Conclusion :** Echocardiography serves as one of the most useful non-invasive screening tool for the diagnosis of Pulmonary Hypertension. Early detection and management is necessary to decrease the morbidity and mortality.

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**Key words :** Hemoglobinopathies, Echocardiography, Pulmonary hypertension.

Hemoglobinopathies recognised in India are Hb E- $\beta$  thalassemia, Sickle-cell Anemia, HbE & HbD<sup>1,2,3</sup>. There is a sharp increase in frequency of  $\beta$ -Thalassaemia trait in Eastern and South Eastern India (Bengal, Odisha and Andhra Pradesh)<sup>4-6</sup>. Common Hemoglobinopathies prevalent in North Bengal are Hb E diseases and E- $\beta$  Thalassaemia.

Cardiovascular complications are among the leading causes of mortality and morbidity in Hemoglobinopathies<sup>7</sup>. In the wide spectrum of Cardiovascular Manifestations, Pulmonary Arterial Hypertension (PAH) holds a prominent place. The Pathophysiology behind Pulmonary Hypertension is Chronic Anemia and Hemolysis. Free Hemoglobin released during Hemolysis scavenges the intrinsic vasodilator Nitric Oxide (NO) and releases arginase<sup>8,9</sup>, which is an enzyme responsible for depletion of L-arginine, a substrate for NO Synthesis. So, there is

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### Editor's Comment :

■ Screening for Pulmonary Hypertension should be an essential component while assessing a patient with Hemoglobinopathy which may be accomplished by Transthoracic Doppler Echocardiography, the most established screening tool for Pulmonary Hypertension in general, widely available, cost-effective. Early detection and management is necessary to decrease the morbidity and mortality.

depletion of NO leading to impaired NO dependent vasodilatation of Pulmonary Vasculature<sup>10</sup>. There is an increased Risk of Thrombosis due to factors released during Red Cell destruction leading to Platelet Activation, Thrombin Generation and tissue factors activation and Obliterative Pulmonary Vasculopathy.

Screening for Pulmonary Hypertension should be an essential component while assessing a patient with Hemoglobinopathy which may be accomplished by Transthoracic Doppler Echocardiography, the most established screening tool for Pulmonary Hypertension in general, widely available, cost-effective<sup>11</sup>. In a landmark study, 32% of adults with HbSS had TRV  $\geq 2.5$  m/s who were associated with a tenfold increase in risk of death<sup>12</sup>.

Common features suggesting presence of PAH are

as following<sup>13</sup>

1. Right atrial enlargement
2. Right ventricular enlargement and dysfunction
3. Small under filled left-sided heart chambers
4. Interventricular septal flattening
5. Tricuspid regurgitation with elevated velocity
6. Reduced Tricuspid Annular Plane Systolic Excursion (TAPSE).

Excursion (TAPSE).

7. PASP: Pulmonary Arterial Systolic Pressure, calculated by assessing TR velocity and Right Atrial Pressure (RAP). RAP is calculated by IVC size and collapsibility. It is easy to measure. If > 2.1 cm size with <50% collapsibility, the estimated RAP is 15 mm of Hg.

$$\text{PASP} = 4 \text{ TRV}^2 + \text{RAP}.$$

Cut off value of PASP is 35 mm Hg<sup>14</sup>.

8. mPAP: Mean Pulmonary Arterial Pressure calculated by assessing PR velocity and Right Atrial Pressure.

mPAP = 4 PRV<sup>2</sup> + RAP. It is relatively easy to measure. Cut off value is 25 mm Hg.

9. AT (RVOT): Right Ventricular Outflow Tract acceleration time is easy to measure, reliable and reproducible. Cut off value is 100 ms. <100 ms is critical.

mPAP is calculated by the formula from AT of RVOT<sup>14</sup>:

$$\text{mPAP} = 79 - (0.45 \times \text{AT}^{\text{RVOT}})$$

The estimation of Pulmonary Hypertension in Hemoglobinopathies is necessary for early detection and management along with the risk stratification and prevention.

#### MATERIALS AND METHODS

This study was Hospital based, Non-interventional, Observational Descriptive, Cross-sectional study, conducted among the indoor patients and those attending Medicine OPD of North Bengal Medical College.

Patients with co existing Pulmonary and Heart Diseases, Connective Tissue Disease, HIV with history of drug and Toxin causing Pulmonary.

Hypertension were excluded from the study.

76 patients of Hemoglobinopathies (>12 years) were evaluated for determining the presence of PAH from 1<sup>st</sup> April, 2019 to 31<sup>st</sup> March, 2020.

Detailed history, general and systemic examination were conducted. Blood investigations like complete Hemogram with Peripheral Blood Smear, Liver Function test, Urea, Creatinine, Fasting and Postprandial Blood Sugar, Serum Iron Profile Study, Hepatitis B and C were done. ECG, Chest X-ray and Echocardiography were performed to see the presence

of features suggestive of PAH in all the study subjects.

Doppler Echocardiography were performed with measurement of Right Atrial Pressure (RAP) by IVC collapsibility, presence of Tricuspid (TR) and Pulmonary Regurgitation (PR). The patients with TR were further evaluated for TR gradient and TR velocity. Pulmonary Arterial Systolic Pressure (PASP) was deducted from TR velocity and RAP. The patients with PR were further evaluated for PR gradient and PR velocity. Mean Pulmonary Arterial Pressure (mPAP) was deducted from PR velocity and RAP. Indirectly, another value of mean Pulmonary Arterial Pressure (mPAP) were deducted from RVOT acceleration time for all patients irrespective of presence of PR.

The entire data was collected with consistency and completeness and entered in Microsoft excel software to prepare a master Table and analysed using various statistical methods like Chi square test, Fisher's Exact, unpaired T-chart and Mann- whitney U test where ever applicable.

#### ANALYSIS AND RESULTS

In this study, majority of the subject were male (56.58%) and the mean age of overall study population was 20.68 ± 9.30 years. (Male 21.14 ± 8.96 years > Female 20.09 ± 9.98 yrs) and most of study population were below 20 years of age. Majority of them belonged to the Rural areas (73.68%) of North Bengal and adjoining areas attending hospital for the treatment of Hemoglobinopathies. 27.63% were Rajbangshi, most of them (23.68%) had Hb E trait. While remaining of the study subject had Hb E β thalassemia (22.37%), followed by, β thalassemia major (17.11%) and Hemoglobin E homozygous state (14.47%) which shows that HbE is predominant in this area.

Pulmonary Hypertension was more prevalent in male patients (37.21%) than female patients (21.21%) but the difference was statistically insignificant. The mean age of patients (18.96 ± 6.35) was lower with PAH. Most of our study subjects with PAH had classically two Cardiovascular Symptoms ie, Shortness of breath (58.33% with p value = 0.037) & syncope (71.43% with p value = 0.024) and both of the symptoms were statistically significantly associated with PAH. Presence of Jaundice (41.30% versus 13.33% with p value = 0.009), weight loss (52.38% versus 21.82% with p value = 0.010) and Anorexia (39.53% versus 18.18% with p value = 0.045) were statistically significantly associated with PAH. Most of the patients with Pulmonary Hypertension had Chelation Therapy (50% versus 26.56%) but it was not statistically significant (p = 0.168). All the patients who had undergone Splenectomy had PAH (100% with



splenectomy *versus* 24.29% without splenectomy) and it was statistically significant. History of blood transfusion were more in mild (31.82%) and moderate (9.09%) PAH and it was statistically significant (p value = 0.038). Mean Pulmonary Arterial Pressure was directly proportional to mean total yearly transfusion (Table 1).

PAH was strongly related with Degree of Anemia and was more prevalent in patients with Severe Anemia (57.14%), 36.84% of Moderate Anemia, 23.81% of Mild Anemic patients. Patients of PAH had lower mean Hemoglobin level than others (7.64 ± 2.46 g/dL in PAH *versus* 9.20 ± 3.02) which was statistically significant (p value = 0.032) and mean Pulmonary Arterial Pressure was inversely related with of Hemoglobin level. Mean rank of Platelets was lower (34.00 with PAH *versus* 40.45 without PAH) and Mean rank of Albumin was lower (35.61) in patients with PAH. Mean rank of Ferritin (52.83 with PAH *versus* 32.28 without PAH) were higher in the patients of PAH. It was observed that mean Pulmonary Arterial Pressure, Pulmonary Arterial Systolic Pressure proportionately increase and RVOT Acceleration time proportionately decrease with mean Ferritin level. Mean iron (197.17 ± 63.32 µg/dL with PAH *versus* 137.62 ± 52.16 without PAH) and mean Transferrin saturation (69.49 ± 20.77% with PAH *versus* 50.16 ± 20.60%) were higher in patients with PAH and they were statistically significant. Mean TIBC (282.17 ± 33.09 µg/dL) was also higher among the patients with PAH.

Table 1 — Prevalence of PAH in various clinical settings

Parameters	% of PAH	
H/O Chelation	Present	50%
	Absent	26.56%
H/O Splenectomy	Present	100%
	Absent	24.29%
Severe Anemia (Hb <8)	Present	42.86%
	Absent	22.92%
Mean total transfusion (>10 U / yr)	Present	44.12%
	Absent	30%
Iron Overload (Ferritin Male >300, Female >200)	Present	36.96%
	Absent	20%
H/O Chelation + Splenectomy	Present	100%
	Absent	25.40%
H/O Splenectomy + Iron Overload	Present	100%
	Absent	20%
H/O Splenectomy + Iron Overload + Severe Anemia (Hb <8)	Present	100%
	Absent	20.69%
Iron Overload + Mean total transfusion (>10 U / yr)	Present	43.33%
	Absent	33.33%
H/O Chelation + Severe Anemia (Hb <8)	Present	50%
	Absent	22.92%
H/O Splenectomy + Iron Overload + Severe Anemia (Hb <8) + Mean transfusion (>10 U/yr)	Present	100%
	Absent	33.33%

Majority of the patients with Pulmonary Hypertension had TR (52.5%) and PR (58.6%) and it was statistically significant. The mean rank of TR Gradient (60.98) and PR Gradient (55.46) were higher in patients with PAH and both of them were statistically significant. The mean AT (110.69 ± 12.93) was lower and mean Right Atrial Pressure (6.21 ± 2.69 mm of Hg) was higher among the patients with PAH and were statistically significant (p value = 0.000 for both) (Table 2).

Most of the patient of Hb E β thalassemia (23.5%) had Moderate Pulmonary Hypertension, while those with Sickle β Thalassemia (33.3%) had Mild Pulmonary Hypertension had but it was not statistically significant (Table 3) There was significant increase in prevalence of PAH due to Splenectomy, mean total transfusion >10 u/yr, severe Anemia, Iron overload and their combinations (Table 4).

DISCUSSION

Seven subtypes of Hemoglobinopathies were identified in this region mainly Hb E trait (23.68%), Hb

Table 2 — Mean Echocardiographic parameters assessing Pulmonary artery pressure in different subgroups

	BTM (n=13) 17.11%	BTT (n=10) 13.16%	EBT (n=17) 22.37%	HEH (n=11) 14.47%	HET (n=18) 23.68%	SBT (n=3) 3.95%	SC (n=4) 5.26%	Total (n=76) 100%
Study population (n = 76)								
RAP (mm of Hg)	4.15± 2.19	3.50± 1.58	5.88± 2.87	3.45± 1.51	4.39± 2.30	3.00± 0.00	3.00± 0.00	4.30± 2.28
AT (mili second)	126.77± 23.28	135.30± 21.88	123.41± 19.17	142.64± 13.82	142.72± 15.42	135.00± 13.23	139.25± 22.56	134.20± 19.68
m PAP(by AT) (mm of Hg)	21.96± 10.37	18.05± 9.65	23.31± 8.58	14.85± 6.13	14.85± 6.91	18.33± 5.86	16.38± 10.06	18.60± 8.75
TR (n = 40)								
	BTM (n=5) 12.5%	BTT (n=5) 12.5%	EBT (n=11) 27.5%	HEH (n=5) 12.5%	HET (n=8) 20%	SBT (n=3) 7.5%	SC (n=3) 7.5%	Total (n=40) 100%
RAP (mm of Hg)	6.00± 2.74	4.00± 2.24	6.09± 3.05	4.00± 2.24	4.88± 2.59	3.00± 0.00	3.00± 0.00	4.85± 2.59
TRV (m/s)	2.62± 0.22	2.34± 0.50	2.59± 0.70	2.66± 0.35	2.11± 0.51	2.40± 0.26	2.43± 0.42	2.45± 0.52
TRG (mm of Hg)	27.60± 4.67	23.00± 8.75	27.81± 13.14	29.00± 7.00	19.00± 8.96	23.67± 4.93	25.00± 7.94	25.05± 9.56
PASP (mm of Hg)	33.52± 6.38	26.80± 6.76	33.62± 15.00	32.70± 7.83	23.73± 11.40	26.17± 4.54	23.63± 8.50	29.12± 10.86
PR (n = 29)								
	BTM (n=3) 10.34%	BTT (n=3) 10.34%	EBT (n=11) 37.94%	HEH (n=4) 13.79%	HET (n=6) 20.69%	SBT (n=1) 3.45%	SC (n=1) 3.45%	Total (n=29) 100%
RAP (mm of Hg)	6.33± 2.89	3.00± 0.00	6.55± 2.91	4.25± 2.50	4.67± 2.58	3.00± 0.00	3.00± 0.00	5.21± 2.72
PRV (m/s)	2.23± 0.64	2.37± 0.21	2.06± 0.54	1.53± 0.31	1.73± 0.37	2.40± 0.00	1.70± 0.00	1.97± 0.50
PRG (mm of Hg)	20.67± 10.21	25.00± 5.29	18.06± 8.33	9.88± 3.47	12.90± 5.00	23.00± 0.00	12.00± 0.00	16.81± 7.86
m PAP(by PR) (mm of Hg)	27.33± 13.43	28.00± 5.29	24.76± 10.20	13.88± 5.45	17.28± 7.33	26.00± 0.00	14.50± 0.00	22.00± 9.56

Table 3 — Degree of Pulmonary hypertension in subtypes of Hemoglobinopathies (n = 76).

Type of Hemoglobinopathies	Pulmonary hypertension			Total	Statistical test
	Absent No. (%)	Mild No. (%)	Moderate No. (%)		
Beta thalassemia major	9 (69.23)	4 (30.77)	0 (0)	13 (100)	Chi square = 15.976, df = 12, p value = 0.192
Beta thalassemia trait	7 (70)	3 (30)	0 (0)	10 (100)	
Hb E Beta thalassemia	9 (52.94)	4 (23.53)	4 (23.53)	17 (100)	
Hb E hemoglobinopathy	8 (72.73)	3 (27.27)	0 (0)	11 (100)	
Hb E trait	15 (83.33)	3 (16.67)	0 (0)	18 (100)	
Sickle beta Thalassemia	2 (66.67)	1(33.33)	0 (0)	3 (100)	
Sickle Cell anemia	3 (75)	1 (25)	0 (0)	4 (100)	
<b>Total</b>	<b>53 (69.74)</b>	<b>19 (25)</b>	<b>4 (5.26)</b>	<b>76 (100)</b>	

Table 4 — Association of degree of PAH with History of Blood Transfusion

Blood transfusion	Pulmonary hypertension			Total	Statistical test
	Absent No. (%)	Mild No. (%)	Moderate No. (%)		
Yes	26 (59.09%)	14 (31.82%)	4 (9.09%)	44 (100%)	Chi square = 6.551, df = 2, p value = 0.038
No	27 (84.38%)	5 (15.62%)	0 (0.0%)	32 (100%)	
<b>Total</b>	<b>53 (69.74%)</b>	<b>19 (25%)</b>	<b>4 (5.26%)</b>	<b>76 (100%)</b>	

E β thalassemia (22.37%) and β Thalassemia major (17.11%). 30.26% of them were having PAH (Mild 25% & Moderate 5.26%). PAH was predominantly seen in Hb E β Thalassemia (47.06%) followed by Sickle beta thalassemia (33.33%) & β Thalassemia major (30.77%)(Fig 1). This finding corroborates with the study done in Thailand by Chueamuangphan N *et al* where that 29.02% of study population of Hemoglobinopathies were having PAH (Mild 17.86%, Mod 7.59%, Severe 3.57%) and among them majority were having E β thalassemia<sup>15</sup>. In our study, 25% of Sickle Cell Disease patients were suffering from PAH. Similar study on PAH in Sickle Cell Disease shows the prevalence ranges from 20 to 40% in Echocardiographic findings<sup>10</sup>. PAH was least prevalent in Hb E Trait (16.67%). Symptoms of Abdominal pain, Fatigability, Bone pain and Anorexia were common in

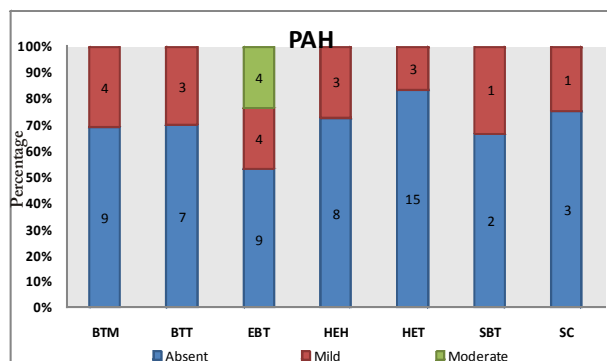


Fig 1 — Degree of Pulmonary hypertension in different subgroups of Hemoglobinopathies (n=76)

overall all the groups of Hemoglobinopathies. Classical Cardiovascular symptoms like shortness of breath and syncope were seen in those with PAH. 15.79% of total population (comprising only BTM 30.77% & EBT 47.06%) are under Chelation Therapy with deferasirox from the hospital. PAH was

more prevalent in the patients receiving Chelation Therapy (50% with chelation therapy vs 26.56% without therapy). Azami M *et al* concluded that 47.22% of total population had PAH and Chelation history was more commonly found in patients of PAH (88.2% with PAH *versus* 73.7%)<sup>16</sup>. 7.89% of study population had undergone Splenectomy surgery and mostly in E β thalassemia (23.53%). Splenectomy was one of the major reason for PAH in Hemoglobinopathies (100% in splenectomised *versus* 24.29%). Similarly, another study by Meera V, Jijina F, Ghosh K, that among 21 splenectomised patients of Hemoglobinopathies 28.57% of subjects had PAH with mPAP of 46.28 ± 28.17 mmHg. The Platelet Count was significantly high in splenectomized patients due higher Pulmonary flow, Thromboembolic occlusion of the vessels and Plexiform Arteriopathy<sup>17</sup>.

Both Mild (31.8%) and Moderate (9.1%) PAH was more common with the history of blood transfusion. Mean Total Transfusion (14.70 ± 9.41 U/yr) was directly associated with the PAH in Hemoglobinopathies. Similarly, Chuncharunee S *et al* concluded in their study that 37.3% of E β Thalassemia patients had PAH and early age of transfusion and total yearly transfusion are directly associated with PAH like our study. PAH was more common with high WBC count (5997.82 with PAH *versus* 5786 without PAH) and Low Platelet Count (Platelet rank 34 with PAH *versus* 40.45). PAH was more predominant in the individuals with Iron overload state (higher value of Ferritin with mean rank 52.83 *versus* 32.28, mean iron 197.17 ± 63.32 µg/dL and mean Transferrin saturation 69.49 ± 20.77% with p value 0.000). Hamdy AM, Zein El Abdin MY, Abdel Hafez MA concluded in their study that, Cardiac dysfunction is a major cause of death in patients with β Thalassemia. Patients with higher serum ferritin level significantly associated with Pulmonary Hypertension<sup>18</sup>. Similar studies also show mean Ferritin level was much higher (3,759.54 + 3267.67 *versus* 2,307.66 + 1886.46) in the patient

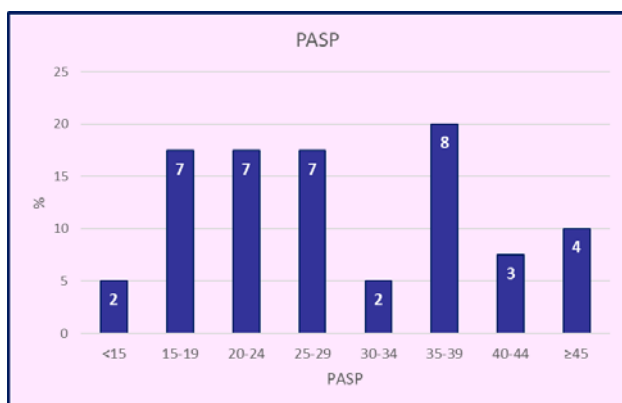


Fig 2 — Distribution of PASP in study population (n=76)

group having PAH<sup>15</sup>.

The mean PASP was  $29.12 \pm 10.86$  mm of Hg with maximum in E  $\beta$  Thalassemia ( $33.62 \pm 15.00$ ) (Fig 2). 38.16% subjects have Pulmonary Regurgitation with PR jet velocity of  $1.97 \pm 0.50$  m/s and PR gradient of  $16.81 \pm 7.86$  mm of Hg with maximum value in  $\beta$  Thalassemia trait and Sickle  $\beta$  Thalassemia. According to estimated mPAP from acceleration time, 26.32% of the population having mPAP  $\geq 25$  mm of Hg with 1.32% of  $> 40$  mm of Hg.

In literature also clinical indicators which increase the PAH in the cases of hemoglobinopathies were E  $\beta$  Thalassemia, Splenectomy (67.69% of patients of PAH), transfusion  $> 6$  U/yr, Ferritin  $> 1000$  ng/dL<sup>15</sup>. Similarly, in our study, we also establish the clinical indicators which increase chance of PAH, like- E  $\beta$  Thalassemia, Splenectomy, Severe Anemia, Transfusion  $> 10$  U/year, Iron Overload state.

### CONCLUSIONS

We conclude from this study that many patients with Hemoglobinopathies have PAH which could be detected by the most widely and easily available Doppler Echocardiography. Most classically, PAH in Hemoglobinopathy is associated with Cardiovascular symptoms like Shortness of Breath and Syncope. Splenectomy increases the prevalence of PAH in the patients of Hemoglobinopathies. Transfusion is a major risk for developing PAH. Mean total transfusion is directly related to the prevalence of PAH. Degree of Anemia Jaundice and Iron Overload State is also associated with degree of PAH.

However, a large scale, multicentric study needs to be conducted to assess the overall prevalence of Pulmonary Hypertension in Hemoglobinopathies and a definitive diagnosis always requires Right Heart Catheterization.

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**Conflict of Interest :** None

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## Original Article

# Study on Bacteriological Profile and Antibiotic Susceptibility Pattern of Clinical Isolates Obtained from COVID-19 Patients with Secondary Infection

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**Background :** Viral respiratory infections increase the risk of secondary bacterial infections owing to their need for hospitalisation, prolonged stay, the practice of Empiric Antimicrobial Prescription. This leads to worrisome Antimicrobial Resistance and such infections have a worse outcome.

**Materials and Methods :** This is a cross-sectional study conducted on patients admitted with COVID-19 at GEMS and Hospital from April, 2021 to June, 2021. The bacteriological profile and susceptibility pattern of the isolates obtained while investigating secondary infections in COVID-19 patients were studied.

**Results :** 132 positive growth samples were collected from ICU and various Wards. Maximum positive growth was found in the Intensive Care Unit (ICU) 36 (27.2%), followed by Surgery Ward 27 (20.5%) and Medicine Ward 27 (20.5%). *Escherichia coli* was most commonly isolated 59 (44.7%) followed by *Klebsiella pneumoniae* 28 (21.2%) and *Pseudomonas aeruginosa* 17 (12.8%). Out of 90 Gram-negative isolates, 25 (27.8%) were found to be Multi-drug Resistant and out of 11 *Staphylococcus aureus* isolates, 5 (45.5%) were MRSA.

**Conclusion :** This study concludes that poor infection control and irrational antibiotic prescription practices play a major role in the development of secondary infections in these patients. Standard practices need to be followed and there should be an implementation of infection prevention control measures and Antimicrobial Stewardship Programs (ASP) must reappraise the current situation.

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**Key words :** Secondary infections, COVID-19, Antimicrobial pattern.

COVID-19 patients are at a higher risk of developing Hospital-Acquired Infections (HAI), both bacterial and fungal. This is due to a prolonged hospital stay, higher chances of requiring ICU and ventilatory support and empirical antibiotics administration to ward off any HAI and also many patients need higher antibiotics as they harbor superbugs. These patients also have impaired ability to clear infections owing to Cytokine Storm which along with the virus facilitate Secondary Bacterial Infection<sup>3,4</sup>, resulting in negative health outcomes.

While Secondary Bacterial Infections are largely a consequence of Immune Susceptibility Viral Infections additionally inflict damage to the mucosal layer, leading to adherence of *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus*

### Editor's Comment :

- Rational use of antibiotics should be strictly followed to avoid the emergence of drug-resistant pathogens.

*influenzae*, with biofilm formation on the linings of the airways<sup>5</sup>. Secondary bacterial infections are common in hospitalised, seriously ill COVID-19 patients. They contribute to 10%-30% of cases with higher frequency in the ICUs<sup>6</sup>. Common bacteria causing Secondary infections to include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *S pneumoniae*, *Neisseria meningitidis*, *H influenzae*, *Proteus*, *Enterobacter*, *Citrobacter* spp., and *Pseudomonas* spp<sup>7</sup>. Recent studies indicate bacterial co-infection upon admission is 3.1–3.5% of COVID-19 patients, while Secondary bacterial infections, are seen in 15% of patients<sup>8-11</sup>. So empirical use of antibiotics is essential in severely ill patients<sup>12,13</sup>. Data obtained from clinical observations in China, indicate COVID-19 patients are most commonly treated with antibiotics (azithromycin, ceftriaxone, vancomycin, moxifloxacin, cefepime,) to reduce the risk of Nosocomial infections as a prophylactic strategy. But Bacterial infections occur despite the prophylactic use of antibiotics, owing to drug resistance to one or more drugs. However, the

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prophylactic use of antibiotics is not recommended by most Healthcare Institutions and Governments around the Globe, due to the rampant increase in antibiotic resistance rates, due to overuse and misuse of antibiotics<sup>14,15</sup>. The risk of secondary infection with Multidrug Resistant (MDR) bacteria poses additional challenges for the treatment of severely sick COVID-19 patients in ICU.

**OBJECTIVES**

The study was conducted with the objectives of

(1) To study the bacteriological profile of clinical isolates obtained from COVID-19 patients with secondary infection.

(2) To evaluate the antibacterial susceptibility pattern of secondary infections in COVID-19 Patients.

**MATERIALS AND METHODS**

This is a cross-sectional study conducted at GEMS and Hospital for 3 months from 1<sup>st</sup> April, 2021 to 30<sup>th</sup> June, 2021.

**Inclusion Criteria :**

Adult cases with RT-PCR positive laboratory-confirmed COVID-19 reports with Secondary Bacterial Infections that were culture positive.

**Exclusion Criteria :**

- Inconclusive laboratory test results (RT-PCR assay).
- Absence of clinical data in the Electronic Patient record system.
- Patient samples did not show significant growth on bacterial culture.

**Data collection :**

The data were collected from Electronic Patient Records of COVID-19 patients. Data including demographic details, comorbidities, date of admission, date of culture-positive results, antimicrobial susceptibility profile of isolates, antibiotics administered, etc. were collected. The collected data were analyzed using descriptive statistics like percentage, proportions, mean and SD.

**RESULTS**

Out of 132 positive growth samples most patients belonged to the age group between 46-60 years followed by 31-45 years (Fig 1). Males were predominantly affected.

The samples were collected from ICU and various Wards. Most of the isolates showing positive growth were obtained from ICU patients 36 (27.2%), followed by Surgery 27 (20.5%) and Medicine 27 (20.5%) (Fig 2).

Out of 132 Positive bacterial cultures, Gram-negative organism 114 (86.4%) were the more compared to gram-positive Organisms 18 (13.6%) (Fig 3).

Among Gram-negative Isolates, *Escherichia coli* 59 (44.7%), was most common followed by *Klebsiella pneumonia* 28 (21.2%) and *Pseudomonas aeruginosa* 17 (12.8%). Among Gram-positive Organism Isolates *Staphylococcus aureus* 11 (8.3%) was most common followed by *Enterococci* 5 (3.8%)(Table 1).

In this study, a total of 90 Gram-negative

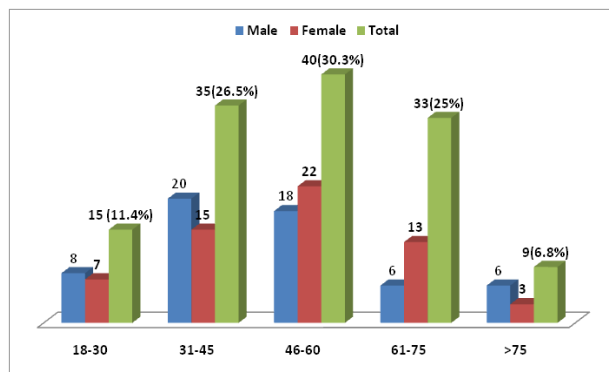


Fig 1 — Gender and Age-wise distribution of COVID-19 patients with secondary infection

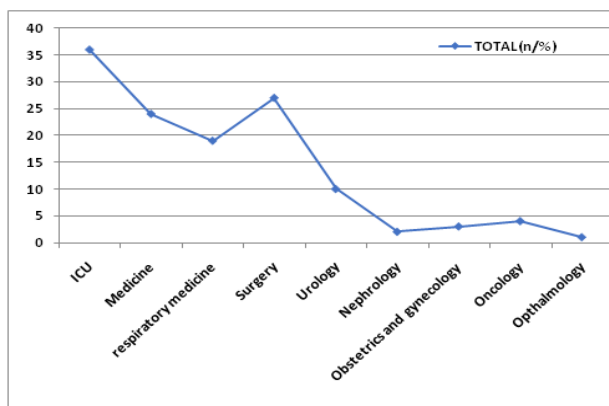


Fig 2 — Distribution of samples from various wards

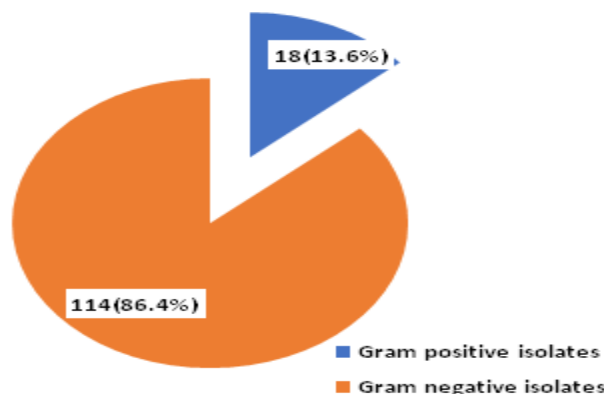


Fig 3 — Distribution of Gram positive and Gram negative isolates (n=132)

Organisms were isolated, 25 (27.8%) were MDR isolates. Out of the 11 *Staphylococcus aureus* Isolates, 5 (45.5%) were MRSA

The antimicrobial susceptibility pattern of Isolated Organisms is presented in tabular form. (Table 2) *Escherichia coli* was predominantly isolated which showed the highest resistance third-generation Cephalosporins, Ceftriaxone 51 (86.4) and Ceftazidime 48 (81.3)

and  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations, piperacillin/tazobactam 47 (79.6).

**DISCUSSION**

This cross-sectional study was conducted on laboratory-confirmed COVID-19 patients who developed a Secondary Bacterial Infection. Patients in whom samples were found to have Colonizing Bacteria without clinically significant infection or contaminants were excluded.

In our study there was a high male to the female ratio similar to several studies which have reported similar results<sup>16,17</sup>, the reason might be due to gender-based lifestyles and behavioral differences like smoking, etc which affect the level of pre-existing diseases such as Heart disease, Chronic lung disease, and cancer.

The most common bacteria detected in the current study were Gram-negative Bacteria 114 (86.4%) followed by Gram-positive Bacteria 18 (13.6%). Gram-negative infections have dominated as far as the type

of organisms is concerned and this is similarly seen in studies reported from other parts of the World describing Superinfections or Secondary Bacterial Infections<sup>14,16</sup>. And also study by Mustafa Karatas, *et al* where *Acinetobacter baumannii* was the main pathogen in the respiratory infections of COVID-19 patients (9.76%)<sup>18</sup>.

Another study also showed Gram-negative Bacteria were commonest (78.03%), eg, *Klebsiella pneumoniae* (29.3%), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *E coli*<sup>19</sup>.

In a study conducted by Surbhi Khurana *et al*, *K pneumoniae* (33.3%) was the predominant pathogen, followed by *A. baumannii* (27.1%)<sup>20</sup>.

It has been found that the COVID pandemic had strong implications for antimicrobial resistance. Indiscriminate use of antibiotics has strongly increased the incidence of Multidrug-resistant Bacteria. In our study, out of the total hospitalised patients with Secondary infections, there were 25 (27.8%) MDR.

Table 1 — Site-Specific Etiological Distribution of Pathogens

Organism Isolated	Blood	Sputum	Urine	Pus	Others	Total(n/%)
<i>Escherichia coli</i>	6 (31.6)	11 (36.7)	28 (71.8)	10 (31.2)	4 (33.3)	59 (44.7%)
<i>Klebsiella pneumoniae</i>	3 (15.8)	12 (40)	5 (12.8)	5 (15.6)	3 (25)	28 (21.2%)
<i>Serratia</i>	1 (5.3)	-	-	-	-	1 (0.8%)
<i>Salmonella spp.</i>	-	-	-	-	1(8.3)	1 (0.8%)
<i>Proteus mirabilis</i>	-	-	-	1 (3.1)	-	1 (0.8%)
<i>Pseudomonas aeruginosa</i>	2 (10.5)	4 (13.3)	2 (5.1)	6 (18.8)	3 (25)	17 (12.8%)
<i>Acinetobacter baumannii</i>	2 (10.5)	3 (10)	-	2 (6.2)	-	7 (5.3%)
<i>Staphylococcus aureus</i>	3 (15.8)	-	-	8 (25)	-	11 (8.3%)
<i>Enterococci</i>	1 (5.3)	-	4 (10.2)	-	-	5 (3.8%)
<i>Streptococcus spp.</i>	1 (5.3)	-	-	-	1 (8.3)	2 (1.5%)
TOTAL	19	30	39	32	12	132

Table 2 — The antimicrobial resistance pattern of isolated organisms is presented in tabular form

Antibiotics	<i>S aureus</i> (n=11)	Strepto-coccus spp.(n=2)	Entero-cocci (n=5)	<i>E coli</i> (n=59)	<i>Klebsiella</i> (n=28)	<i>Serratia</i> (n=1)	<i>Salmonella</i> (n=1)	<i>Pseudo-monas</i> (n=17)	<i>Acinetobacter baumannii</i> (n=7)	<i>Proteus miabilis</i> (n=1)
Penicillin	8 (72.7)	2 (100)	4 (80)	-	-	-	-	-	-	-
Amoxiclav	-	-	1 (20)	-	-	-	-	-	-	-
Piperacillin-Tazobactam	-	-	-	47 (79.6)	23 (82.1)	0	-	7(41.1)	2 (28.6)	0
Cefoxitin	5 (45.5%)	-	-	-	-	-	-	-	-	-
Cefuroxime	-	-	-	-	17 (60.7)	1 (100)	0	8 (47.0)	5 (71.4)	0
Ceftazidime	-	-	-	48 (81.3)	15 (53.5)	1 (100)	0	3 (17.6)	6 (85.7)	1 (100)
Ceftriaxone	4 (36.3)	1 (50)	2 (40)	51 (86.4)	23 (82.1)	1 (100)	0	9 (52.9)	6 (85.7)	1 (100)
Gentamicin	5 (45.4)	0	1 (20)	51 (86.4)	24 (85.7)	0	1 (100)	8 (47.0)	5 (71.4)	1 (100)
Amikacin	3(27.2)	0	1 (20)	49 (83.0)	23 (82.1)	0	1 (100)	7 (41.2)	5 (71.4)	1 (100)
Ciprofloxacin	4 (36.3)	1 (50)	1 (20)	38 (64.4)	18 (64.2)	1 (100)	1 (100)	11 (64.7)	7 (100)	1 (100)
Clindamycin	0	0	2 (40)	-	-	-	-	-	-	-
Chloramphenicol	9 (81.8)	1 (50)	1 (20)	-	-	-	-	-	-	-
Erythromycin	8 (72.7)	1 (50)	1 (20)	-	-	-	-	-	-	-
Linezolid	0	0	0	-	-	-	-	-	-	-
Vancomycin	0	0	0	-	-	-	-	-	-	-
Imipenem	-	-	-	4 (6.8)	3 (10.7)	0	0	3 (17.6)	2 (28.6)	0
Meropenem	-	-	-	3 (5)	2 (7.1)	0	0	4 (23.5)	1 (14.3)	0
Polymyxin B	-	-	-	2 (3.3)	1 (3.6)	0	0	2 (11.8)	0	-
Colistin	-	-	-	2(3.3)	1 (3.6)	0	0	1 ( 5.9)	0	-



*Escherichia coli* was predominantly isolated which showed the highest resistance to third-generation cephalosporins, ceftriaxone 51 (86.4%) and ceftazidime 48(81.3%) and  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations, piperacillin/tazobactam 47 (79.6%).

Not only overuse of antibiotics but intrinsic characteristics of patients themselves also have a strong impact on antimicrobial resistance. As hospitalized COVID-19 patients often are comorbid subjects who went through several hospitalizations during previous months, leading to colonization by Multiple Drug Resistant (MDR) and also Impaired Immune System. All these factors together lead to a full-blown infection with resistant bacteria. Several studies have indicated that not only use of excessive and inappropriate use of antibiotics but also hygiene education, social distancing, wearing of face masks, regular hand washing, isolation of infected cases, Personal Protective Equipment (PPE) employments, contact precautions are strongly recommended, however evidence for this is weak.

#### Limitations :

As this study was conducted in a single center, therefore findings can't be generalized to other parts of the Country, as the prevalence of MDR pathogens is often specific to each Hospital.

#### Conclusion :

In our study maximum, positive growth was isolated from ICU 36 (27.2%), *Escherichia coli* was most commonly isolated 59(44.7%). Out of 90 Gram-negative isolates, 25(27.8%) were found to be MDR producers and among 11 *Staphylococcus aureus*, 5(45.5%) were Methicillin-Resistant *Staphylococcus Aureus* (MRSA).

From this study it has been found that poor infection control and irrational antibiotic use lead to Secondary infections, standard practices in ICU need to be followed, (use of PPEs, double gloves, frequent hand washing, etc ), there should be an implementation of Infection Prevention Control Measures in hospitals and Antimicrobial Stewardship Programs (ASP) should take effort to measure and improve antibiotic prescribing and use to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use and combat antibiotic resistance and clinicians could also de-escalate treatment as soon as patients condition improves. All these together may decrease the overall mortality rate.

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## Original Article

# Proportion of Consanguineous Marriages in Community and Factors Affecting Pregnancy Outcome : A Hospital based Study in Ahmedabad City, Gujarat

Vandana K Saini<sup>1</sup>, Divyesh Panchal<sup>2</sup>, Jaydeep D Kagathara<sup>3</sup> Arpit Chelabhai Prajapati<sup>4</sup>

**Objectives :** To find out (i) the proportion and the types of consanguinity and (ii) its correlation with fetal loss, neonatal deaths, complication related to obstetric and congenital abnormalities.

**Methods :** All the delivered women at Tertiary Care Hospital were included in the cross sectional study during the study period. Total sample size was 6775. Information regarding educational status, occupation, consanguinity and pregnancy outcome was collected.

**Results :** 17% consanguinity was found in selected people and among these marriages, 59.8% were between first cousins. There was highly significant difference observed between the consanguineous status of women and pregnancy outcome (Congenital malformations, abortion, Intrauterine death).

**Conclusion:** The incidence of congenital abnormalities, Intrauterine Device (IUD) and abortion was found higher in Consanguineous marriages. There is a need to improve public awareness regarding problems related to Consanguineous marriages.

[J Indian Med Assoc 2022; 120(3): 33-5]

**Key words :** Consanguineous marriage, Pregnancy outcome, Abortion, Birth defect.

In India like Countries, marriage is a Religious duty in Society. Consanguineous is common among some Religion or community. The world Consanguineous comes from the two Latin words 'Con' meaning shared and 'Sanguis' meaning blood. Consanguineous relationship shows the relation between couple who share an antecedent or share genes. Such type of marriages are favoured by various people of the Community usually bound to traditional customs beliefs and to keep all property in united form within the same family. The most of the Consanguineous marriages (20% to 50%) found in North of African, Asian Countries etc. Usually it was associated with loose Economic status, Rural residence area<sup>1,2</sup>. The incidence of Consanguineous marriage found in India is almost 5-60% and uncle-niece are the more frequently occurring relationship in Indian Population<sup>3</sup>.

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### Editor's Comment :

■ Consanguineous relationship is associated with an increased risk for congenital abnormalities among newborn so there is need for public literacy on consanguinity and this may be achieved by providing proper counselling and health education among people. Also there is need to provide training to health care workers on all health and social issues related to consanguinity.

In India the main reason for this marriage are Stronger Family Ties, the Integrity of Estates. But the current debate in Medical Science is on the health implication of the Consanguineous marriages.

Those couples who were having Consanguineous marriages are at Major Risk for Bipolar Psychiatric Disorders. This Marital System of India has been repaired as an important factor in the appearance of Autosomal Recessive Disease and Congenital Anomalies, Sterility, Infant mortality child deaths, Spontaneous abortion and Stillbirth<sup>4</sup>.

### MATERIAL AND METHODS

Current research study was carried out at Institutional Teaching Hospital, Obstetrics and Gynaecology Department, Ahmedabad. All the delivered women were included in the cross-sectional study. The total sample size (women) was 6775 during

a period of 16 months. Details regarding educational status, occupations, consanguinity and pregnancy outcome were collected through interview. History regarding Abortions, Obstetrical complication, Still birth, Neonatal deaths and Congenital abnormalities developed among children was collected through interview from selected delivered females. Inclusion criteria was all admitted women at Institute. Those patients who had not given consent for the study were excluded from the study. Data was entered in MS Excel and were analyzed through MS Excel and Epi info. Percentage (%), Chi-square test were applied for the statistical calculation. 'p' value considered statistically significant when p value is less than 0.05.

### RESULTS

As stated in Table 1, 92.61% of delivered participants belongs to 18 to 30 years of age group. Of all participants, 62.42% participants were illiterate and only 5.82% participants were having higher educational status. Total number of deliveries were 6775, out of which Hindus are 2476 (36.8%) and Muslims are 4267 (62.9%) and other are 42 (0.61%). Out of 6775 women, consanguinity were found in 17.4% of the marriage. Among Muslims, consanguinity was higher in frequency (17.21%) than Hindus (0.17%). This difference between Consanguinity and Religion was statistically significant ( $<0.00001$ ). (Table 1)

Table 2 shows that majority of the Consanguineous marriage were found in Muslim out of them marriage between 1<sup>st</sup> cousin marriage was 59.3%, uncle-niece marriage was 33.81% while 5.67% were having further distinct relations of the marriage while in Hindus it was almost nil (Table 2).

In Consanguineous marriage, proportion of abortion were 21.1% and in Non-consanguineous, abortion was 12.3%. It showed abortion were in Consanguineous Group statistically significantly higher as compared to Non-consanguineous Group. The p value was highly statistically significant ( $p < 0.00001$ ). Total number of Intrauterine Deaths (IUD) were 185 out of which 59 (5.0%) were Consanguineous and 126 (2.3%) are Non-consanguineous. There was significantly difference in the frequency of IUD between the consanguineous and Non-consanguineous groups. (Table 3).

In 81 (6.9%) Congenital malformation are observed in Consanguineous groups and 153 (2.7%) in Non-consanguineous group. Incidence of anomalies in

present study are 0.4% (234). Present study observed that Congenital Abnormalities were statistically significantly higher in Consanguineous Group ( $p$  value  $<0.01$ ).

### DISCUSSION

Majority of women belongs to the age group between 26 to 30 years, 62.42% illiterate. Total number of deliveries were 6775, out of which Muslims were 4267 (62.9%). Out of 6775 women, Consanguinity were found in 17.4% of the married women. Among Muslims women (17.21%), Consanguinity was higher than Hindus (0.17%). This difference between Consanguinity and Religion was statistically significant ( $<0.00001$ ).

Current study found that proportion of Consanguinity was 17.4%, which is less as compared to many other studies<sup>5</sup>.

Due to modern era, such Consanguineous marriages may be on decline in worldwide. Muslim Community showed large numbers of Consanguineous marriage as compared to Hindu Community.

The common type of Consanguineous marriage among current study participants were between first cousins (59.4%). Such results were as similar as to the results observed in various other study<sup>6-8</sup>. All the cousin marriages were between cross-cousin. No parallel cousin was observed.

Kerkeni *et al*<sup>9</sup> reported that the rate of Spontaneous abortion and still births were not correlated with Consanguinity. In this study, there was significance difference in the number of IUD and Abortion between Consanguineous and Non-consanguineous groups.

Jain *et al*<sup>10</sup> showed that Consanguineous marriage had no statistical significant effect on fetal losses but that the numbers of Consanguineous marriages were higher with Congenital Abnormality. Kulkarni *et al*<sup>11</sup> observed that Congenital Anomalies and still births were significantly more in Consanguineous marriage and similar results were found in the current study ( $p$  values  $<0.05$ ).

Present study observed that Congenital Abnormalities were significantly higher in couple having consanguineous marriage ( $p$  value  $<0.00001$ ).

The new cases of Congenital Abnormalities were 2.8% or 28/1000 delivery, although we think it is under estimated. The rate of Consanguineous marriages is very high (63.4%) in the population<sup>12</sup>.



### CONCLUSION

The incidence of Congenital Abnormalities, IUD and Abortion was found higher in Consanguineous marriages. There is a need to improve people awareness regarding problems related to Consanguineous marriages. Hence current research suggests that steps must be taken to communicate people about the problem of marrying to close relative. It is better to avoid Consanguineous marriage in families due to risk of developing the Congenital Fetal Abnormalities. Educational programs among people on the negative pregnancy outcome of Consanguineous marriage need to be continued and effort should be made to reduce the exposure to associated factors.

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## Original Article

# Comparative Analysis of Amoebic Liver Abscess versus Pyogenic Liver Abscess on Clinical and Investigative Consequences

Sangeeta Ghosh<sup>1</sup>, Pritin Kumar Bera<sup>2</sup>, Avijit Saha<sup>3</sup>, Tapas Kumar Sur<sup>4</sup>

An attempt was made to compare the analysis of investigative parameters to distinguish Amoebic Liver Abscess (ALA) from Pyogenic Liver Abscess (PLA). This study was carried out at Calcutta National Medical College & Hospital, Kolkata 700014. Patients were included with signs and symptoms suggestive of Liver Abscesses. The investigations of Serological, Hematological, Biochemical, Radiological and CT scan were done. Antimicrobial Therapy, Image Guided Percutaneous Aspirations/Drainage or Open surgical Drainage was performed and checked in follow-up visits up to 3 months. The highest incidences of Liver Abscess (53.3%) were encountered in alcoholic male. Fever and Abdominal Pain were common in both ALA and PLA. Hepatomegaly was significantly high ( $p < 0.05$ ) in PLA (64.2%) than ALA (37.5%), but jaundice was only noted in PLA (22.2%). *E coli*, *K pneumonia* and *S aureus* were confirmed in PLA. Alkaline Phosphatase was significantly high ( $p < 0.05$ ) in PLA. Right sided pleural effusion was noted in Chest X-ray of 50% cases. USG studies measured 70% Solitary Abscesses with 5-10 cm in the Right Lobe. Partial resolution occurred in 28.6% of PLA and 31.2% of ALA. USG and Serological Tests are recommended and Conservative Management should be followed for ALA and invasive treatment for PLA patients.

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**Key words :** Liver Abscess, USG, Microbes, Surgical drainage

Liver Abscess remains an important clinical problem since the time period of Hippocrates (circa 400 BC)<sup>1,2</sup>. Based on etiology, there are three major varieties of Liver Abscess - Pyogenic, Amoebic and Fungal. Amoebic Liver Abscess (ALA) is most familiar extra intestinal site of infection in under developed Countries, like South-East Asia, Africa, Mexico, Venezuela, Colombia etc. The highest incident of Liver Abscess observed in Asia, where rates can be as high as 21 per 100000 inhabitants per year<sup>3,4</sup>. However, Pyogenic Liver Abscess (PLA) is relatively common in developed Countries, including United States. Biliary Tract Disease (Cholelithiasis, Obstructing tumors, Congenital Biliary Tree Anomalies etc), Portal Vein seeding (Appendicitis, Diverticulitis) or Inflammatory Intestinal Diseases are the most common etiology of PLA<sup>5</sup>. PLA may also be caused by a variety of organisms, including *Escherichia coli*, *K pneumoniae*, *Enterococcus* and *Streptococcus* species, while, *Entamoeba histolytica* is solely responsible for ALA.

### Editor's Comment :

- All symptomatic Liver Abscesses patients should be examined USG and serological tests for *E histolytica*, *E coli*, *K pneumoniae* and *S aureus* before starting the treatment.
- Conservative management should be followed for ALA and invasive treatment including percutaneous aspiration, pigtail catheter insertion, Laparotomy for PLA patients as early as possible.

*K pneumoniae* is also associated with Colorectal Carcinoma<sup>6</sup>. It has been reported that ALA occurred in 3-9% of all patients with Amoebiasis, mainly in areas with poor sanitation and hygiene. In India, it affects more than 15% of the population. The mortality rate has been estimated to be around 0.2-2% in adults and up to 26% in children<sup>7</sup>. The major Risk Factors for ALA are Diabetes, Alcohol Consumption, Malignancies, Malnutrition and HIV infection<sup>8,9</sup>. Eventually during invasion, Amoeba penetrates portal vein and Transported through portal circulation to Liver, where Trophozoites (growing and feeding stage of the parasite) not only Accelerate Thrombosis and Infarction to Hepatic Tissues, but also lead to Cytolysis<sup>10</sup>. The most of the ALA are solitary lesions and more often found in the Right Lobe than the left, whereas, 18%-66% of PLA are Cryptogenic, with no underlying cause identified<sup>11</sup>. The clinical diagnosis is difficult to perform since the symptoms are usually vague and nonspecific. Leukocytosis, elevated inflammatory markers, increased Alkaline Phosphatase and abnormal Liver Function Tests are frequently observed in both ALA

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and PLA. Blood culture, Antigen test, Ultrasonography (USG) and Computed Tomography (CT) scanning are usually used to confirm Liver Abscess<sup>12</sup>. Even though metronidazole, tinidazole, ornidazole, nitazoxanide, chloroquine are the choice of medicine to treat ALA, but image guided Percutaneous Drainage along with Targeted Antimicrobial Therapy is helpful treat PLA<sup>13,14</sup>. In spite of considerable attempts to differentiate, but till no reliable clinical characteristics identified for ALA versus PLA. The common clinical symptoms of liver abscess are Fever, Jaundice and Right upper quadrant pain and Tenderness<sup>4</sup>. Therefore, the objective of the present study was to find out the probable differentiating clinical and microbiological features between ALA and PLA in hospital set up.

#### MATERIALS AND METHODS

This prospective longitudinal study was conducted in the Department of General Surgery, Calcutta National Medical College and Hospital (CNMC&H), Kolkata, India in the time period of January, 2014 to December, 2014 after receiving the approval from Institutional Ethical Committee (IEC/CNMC/58 date 3/1/2014). Adult patients of either sex with Liver Abscess diagnosed clinically and/or Radiologically (USG/CT) were screened thoroughly before included in the study. The exclusion criteria of the present study were (i) Traumatic liver abscess, (ii) Past history of liver abscess, (iii) Liver abscess in paediatric age group, (iv) Abscess coexisting with malignancy of Liver and (v) Indeterminate and Mixed Etiology Liver Abscess.

ALA was confirmed by positive ELISA test for *Entamoeba histolytica* trophozoites and in blood and aspirated pus, while PLA was confirmed by positive cultures of blood and pus. The selected patients were divided into two groups: ALA and PLA. The Clinical Symptoms (Fever, Pain in abdomen, Abdominal swelling, Jaundice etc) were recorded. Routine Hematological (Hb%, TC, DC, ESR, PT) and Biochemical (Glucose, LFT, Urea, Creatinine) investigations were conducted. The Culture and Sensitivity test were done in blood and aspirated pus. X-ray (Chest, Abdomen), USG (Abdomen) and CT scan (Abdomen if required) were also done. Once the diagnosis of Liver Abscess was confirmed, broad spectrum parenteral antibiotics along with a nitroimidazole compound were started. If condition did not improve, then drainage of the Abscess Cavity was done on first attempt. Image guided Percutaneous Aspiration or Pig Tail Catheter Drainage or open surgical drainage was conducted as per patient's health condition. Laparotomy was indicated for Ruptured Amoebic Abscesses or Abscess with an underlying

or associated Abdominal Pathology. The parametric and on parametric results were presented as descriptive statistics and analysed using software based statistical package (SPSS v.20, IBM, USA).

#### RESULTS

Table 1 represented demographic details of selected patients in the study. Among 30 cases of Liver Abscess, 53.3% was of ALA group and 46.7% was of PLA group. Overall, there was 23 males (76.7%) and 7 females (23.3%). Prior history of Alcohol intake was reported in 56.7% of total study population. Maximum patients were coming from the age group of 20-40 years, similar to ALA group (62.5%). Among PLA the maximum duration of symptoms was 11-20 days (42.9%) but of ALA it was prolonged ( $\geq 21$  days). Although, the duration of symptoms of PLA and ALA was slightly differed from each other but these changes was not statistically significant.

The most common clinical feature encountered among Liver Abscess was Fever (76.7%) followed by Pain in Abdomen (73.3%). Fever was present in 85.8% cases of PLA and 68.8% cases of ALA; while, Pain in abdomen was present in 85.8% cases of PLA and 62.5% cases of ALA. Abdominal Swelling or Hepatomegaly was present in 64.2% cases of PLA and 37.5% cases of ALA. Jaundice was present in 22.2% cases of PLA and none in ALA (Table 1).

Laboratory investigations exhibited 20% patients were anaemic (Hb% <10 gm/dl), 13.3% Diabetic (Fasting Blood Glucose >200 mg/dl), 13.3% detected jaundice (bilirubin <2gm/dl) and 33.3% leukocytosis (WBC >11,000 cells/cc). Alkaline phosphatase (AKP <300 IU) was elevated in 53.3% and Prothrombin time (PT >20 sec) in 10.0% of the cases (Fig 1).

Table 1 — Demographic details of selected patients

	Total	ALA	PLA
Number of Patients	30	16	14
Male	23	10	12
Female	7	6	2
Age group:			
20-40 years	16	10	6
41-60 years	12	6	6
$\geq 60$ yrs	2	0	2
<b>Duration of symptoms :</b>			
$\leq 5$ days	3	1	2
6-10 days	7	3	4
11-20 days	12	6	6
$\geq 21$ days	8	6	2
<b>Clinical symptoms :</b>			
Pain in abdomen	22	10	12
Fever	23	11	12
Abdominal swelling	15	6	9
Jaundice	4	0	4
Alcohol addiction	17	9	8



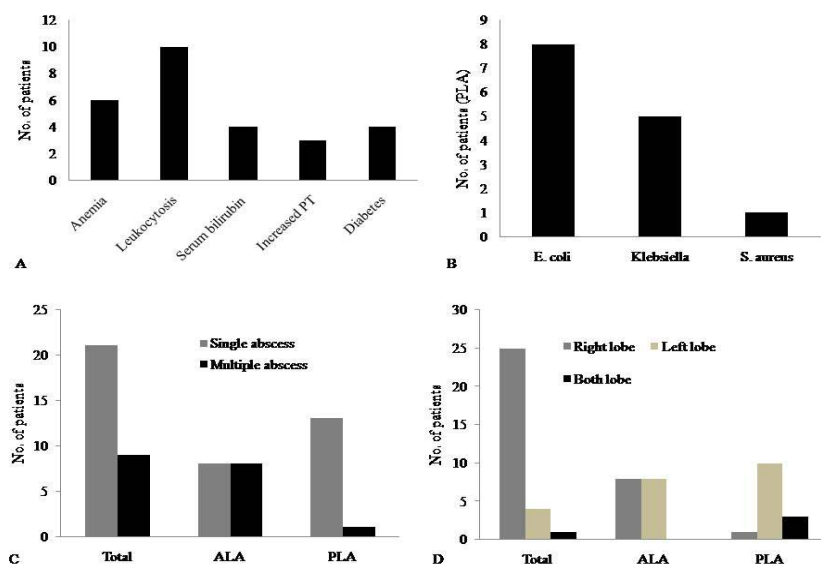


Fig 1 — Laboratory investigations of liver abscess patients [A] Incidences of comorbidity; [B] Incidences of bacterial invasion; [C] Number of abscess; [D] Area of infected hepatic lobe

Microbial investigations (blood culture) showed negative results for all patients of ALA group, but 42.9% were positive of PLA group (Fig 1). Most common organism present in Blood Cultured of PLA was *E coli* (50.0%), followed by *Klebsiella* (28.5%) and *S aureus* (7.1%). In pus culture of PLA group, 14.2% cases were polymicrobial (*E coli* and *Klebsiella*).

Pleural effusions with obliteration of costophrenic

angle were noted in chest X-ray of 50% patients (Fig 2). USG studies revealed that the right lobe of liver was mostly affected in both ALA (100%) and PLA (64.2%) patients (Fig 2). However, single abscess were noticed in 92.9% of PLA and 50% of ALA. Moreover, maximum diameter (in greatest dimension) of Liver Abscess was measured 5-10 cm in PLA, while 50% of ALA cases showed <5cm.

Among 30 cases of Liver Abscess, 33.3% cases were managed by Medical Therapy alone. Percutaneous drainage was performed in 57.2% cases of PLA and 42.8% cases of PLA required Open Surgical Drainage (Fig 2). None of the PLA was adequately treated by Conservative approach. However in case of ALA conservative management was most commonly performed. In the follow up period of 3 months, partial resolution of Liver Abscess was occurred in 28.6% cases of PLA and 31.2% cases of ALA, while the rates of complete resolution were 71.4% and 68.8% in PLA group and ALA group respectively.

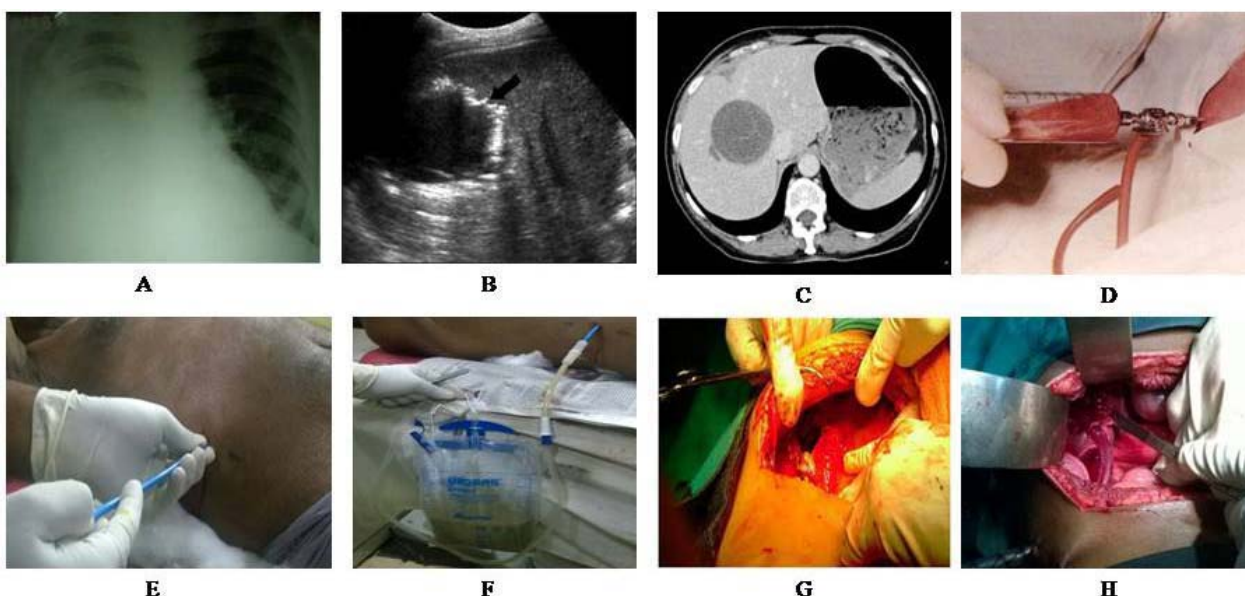


Fig 2 — Findings of liver abscess and invasive treatment management [A] Chest X-Ray showing elevated right hemidiaphragm with pleural effusion; [B] Abdominal USG showing single abscess cavity; [C] Abdominal CT scan showing single abscess cavity; [D] Image guided percutaneous aspiration; [E] Image guided Pigtail drainage; [F] Image guided pigtail catheter drainage; [G] Open surgical drainage: showing abscess cavity; [H] Open surgical drainage: drain in abscess cavity

## DISCUSSION

Liver abscesses, both Amoebic and Pyogenic continue to be an important reason of mortality in the Tropical Countries. Most of the Liver Abscess complications include Sepsis, Emphysema and Peritonitis. The clinical diagnosis is difficult to perform since the symptoms are usually vague and nonspecific. In this study patients of both Amoebic (53.3%) and Pyogenic (46.7%) Liver Abscess were examined and evaluated for etiological and predisposing features, signs and symptoms, laboratory test results, radiological findings and various treatment modalities. Tubercular and Fungal Liver Abscess not incorporated in this study. The age groups of the patients were varied from 26-66 years. The highest incidence was noted in the age group of 20-40 years (53.3%) followed by age group of 41-60 years (40.0%). Mean age in this study was observed 41.6 years. Other studies in Indian population also supported this findings<sup>15,16</sup>. Present study exhibited male predominance between ALA and PLA, which may be attributed due to the different lifestyles of Men and Women of this country. Besides male predominance, alcoholic patients were also noted in both ALA (64.2%) and PLA (57.1%) which clearly indicated Alcoholism is one of the major predisposing risks in Liver Abscess. In other study, alcoholism was found in 70% of liver abscess<sup>17</sup>. In fact, the onset of liver abscess is not only subjected to dissimilarities depending upon type, location and quantity of abscess, but it may be acute and clinically undetectable. In this study, the maximum duration of symptoms was noted 11-20 days in cases of PLA and  $\geq 21$  days in cases of ALA, similar to other reports<sup>18</sup>. Most common presenting complaints were Fever and Abdominal Pain. Abdominal swelling or Hepatomegaly was exhibited in 64.2% cases of PLA and 37.5% cases of ALA. This findings correlate with other studies, where clinically Hepatomegaly had noted in 72% cases<sup>18</sup>. Clinically jaundice was observed in only 22.2% cases of PLA but none in ALA. Furthermore, 20% patients were anaemic, 33.3% Leukocytosis and 10% Diabetic. Neutrophilic Pleocytosis was also noted in both types of Liver Abscesses. Hyperbilirubinemia (Serum Bilirubin  $>2$  mg/dl) were observed in 13.3% of cases, similar to earlier findings<sup>19</sup>. No other Liver enzymes, but only Alkaline Phosphatase (ALP) were raised in 53.3% of Liver Abscess patients. In another study, Sharma and Ahuja (2003) have been reported elevated ALP (2-4 times) in 60-80% of cases of Liver Abscess<sup>15</sup>. Hence, it might suggest that the elevated level of ALP is one of the common prognostic indicators in any type of Liver Abscess. Anaemia and Jaundice

were more marked in Pyogenic Liver Abscess Cases.

In the present study, out of the 30 cases of Liver Abscesses, 20 cases had subjected to invasive treatment; while pus culture has shown positive in 12 cases. Most common organisms present in cultured was *E coli* (50.0%) followed by *Klebsiella* (28.5%) and *S aureus* (7.1%). Although, Blood Culture Test exhibited sensitivity in 42% of PLA patients, while *E coli* marked most familiar pathogen. Chung *et al* (2007) reported *E coli* and *Klebsiella* to be the most common organisms present in PLA pus and blood cultured<sup>20</sup>.

Present study demonstrated that PA views of Chest X-ray were significantly abnormal (50%) in both ALA and PLA with Right Sided Pleural Effusion (43.3%) and Elevated Right Hemi Diaphragm. Furthermore, USG in abdomen exhibited 70% Solitary Abscess in exclusively on Right Lobe. Most common size of Abscess in PLA was noted 5-10 cm, while in ALA it was less than 5 cm. In other studies, Solitary Abscesses were found in 72-80% and right lobe association was noted in 65-72% of cases<sup>21,22</sup>. Abdominal USG is still the diagnostic modality of choice for hepatic pathologies including liver abscess, although CT scanning has now showed better sensitivity (97% sensitive) than USG (85% sensitive) in Liver Abscess detection. Because, sagittal plane of scan precisely defined the segments involved and accurately localize the Abscess in Liver<sup>23</sup>. Present observation reported the involvement of 6th and 7th segments in Right Lobe. The predilection of liver abscess in Right Lobe is because of streaming effect in portal circulation, which receives most of blood draining from right colon, the primary site of Intestinal Amoebiasis<sup>24</sup>.

Surgical drainage of Liver Abscesses has been an accepted therapy for decades. The diagnosis and treatment management of Liver Abscess has changed due to advances in imaging techniques. In the present study, the conservative management was done on 33% cases. All the cases of ALA were treated conservatively. None of the PLA was treated by conservative management alone. Any form of invasive treatment was needed in all PLA. Therefore, it may assumed that conservative medical management of uncomplicated ALA is safe but patients who fail to respond to Medical Therapy should be considered for USG guided Percutaneous Aspiration. Percutaneous Needle Aspiration is safe, rapid, effective method of treating Liver Abscess<sup>25,26</sup>. In this study, percutaneous needle aspiration was used in 46.7% of patients. Majority of patients showed drastic improvements in their symptoms and signs within 72 h of the Aspiration.

Laparotomy was performed in 20% of Liver Abscess. Peritonitis and Cholelithesis were reported in PLA. Image Guided Percutaneous Aspiration/Catheter Drainage was the main form of Surgical Therapy, although most of them were under coverage with antibiotics and responded to Percutaneous Aspiration/Catheter Drainage and Antimicrobials. Partial resolution occurred in 28.6% cases of PLA and 31.2% cases of ALA within 3 months. On the other hand the rates of complete resolution had 71.4% and 68.8% in PLA and ALA respectively. Success rate of complete resolution depends on early detection, complete distinction and confirmation of types of Liver Abscess present.

### CONCLUSION

From the above discussion, it may conclude that ALA is more common than PLA. Abdominal USG and Serological Tests of Pus and/or blood can clearly distinguish PLA from ALA. Furthermore, conservative management is safe for ALA but sort of invasive treatment including Percutaneous Aspiration, Pigtail Catheter Insertion, or Laparotomy should be followed for PLA patients.

**Limitations:** The study was conducted in a single centre and small number of population. Sample size is too small to draw any conclusion. Therefore, a detailed study is recommended.

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## Original Article

# An Observational Study on Pharmacoeconomics and Prescription Pattern of Drugs Used in Diabetes Mellitus (Type II) in a Tertiary Care Hospital of Eastern India

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**Background :** Diabetic patients need to consume multiple medications at a time due to presence of Hyperglycemia, its pathophysiology and complications. In this context the compliance of the patient depends on the cost of therapy, The conduction of this study was faced with limitations like the COVID-19 pandemic. In spite of that, we have decided to conduct this challenging task by analyzing the pattern of prescriptions and comparing the prices of Anti-diabetic Drugs in our Tertiary Care Teaching Hospital.

**Objective :** • To study the pattern of prescription writing in Type II Diabetes Mellitus and its association with the extent of control of the disease. • To analyze and compare the cost of different Anti-diabetic Drugs in Type II Diabetes Mellitus in a Tertiary Care Hospital.

**Material and Methods :** This is an observational study of descriptive type. It is prospective in nature. All the demographic characteristics of the patient, disease profile, drug profile and prescription profile were included in the case report form. A photocopy of the patient's Pharmacy Bill was collected from the indoor Pharmacy for analysis.

**Result :** The mean number of anti-diabetic medications prescribed in Generic name was 3.0(±2.12) while the mean number of drugs prescribed in Brand name was 4.02(±1.99). The average number of prescribed injectable drugs was 0.11 (±0.31) with p-value=0.012 and the mean number of prescribed Fixed Dose Combinations (FDCs) was 0.16 (±0.42) with p-value=0.005. The total number of prescribed Anti-diabetic medications was higher in presently Hyperglycemic patients under Anti-diabetic Therapy compared to presently Normoglycemic patients under Anti-diabetic Therapy. A weak positive correlation was found between family income per capita and total cost of treatment.

**Conclusion:** The total cost of treatment in presently Hyperglycemic patients under Anti-diabetic Therapy is relatively high due to prescription of more number of Anti-diabetic Medications. Metformin is the most common Anti-diabetic agent used in clinical practice and oral route of Drug Administration is mostly preferred in the OPD settings.

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**Key words :** Diabetes Mellitus, Pharmacoeconomics, prescription pattern, Treatment.

**D**iabetes Mellitus (DM) refers to a group of Metabolic Disorders, which is characterized by Hyperglycemia occurring due to a defect in the secretion of Insulin or in its function or a combination of the both<sup>1</sup>. According to American Diabetic Association Classification, a diagnosis of Diabetes Mellitus is characterized by at least any 1 of the following criteria– Fasting Plasma Glucose (FPG)  $\geq 126$  mg/dl (7.0 mmol/l), 2-hours post-load value in the Oral Glucose Tolerance Test (OGTT)  $\geq 200$  mg/dl

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### Editor's Comment :

- The economic burden of treatment in hyperglycemic patients under anti-diabetic therapy is significantly high.
- Thus, rational prescription as well as physician knowledge of current drug prices is necessary to ensure patient compliance specially those belonging to lower socioeconomic classes.

(11.1 mmol/l), a random Plasma Glucose Level  $\geq 200$  mg/dl (11.1 mmol/l) with symptoms of diabetes and/or HbA1c levels  $\geq 6.5\%$ <sup>1</sup>. Chronic nature of Diabetes Mellitus requires life-long treatment in order to maintain the normal Glucose levels in blood and may lead to several complications. This may degrade the quality of life. In 381 million people had been diagnosed with Diabetes Worldwide as per report of International Diabetic Association (2013) After years of careful observation, it can be concluded that its swiftly growing incidence expected to double by 2030<sup>2</sup>. India is estimated to have 109 million individuals affected

with Diabetes by 2035, as stated by the Indian Heart Association and has been labeled as the "Diabetes Capital of the World"<sup>3</sup>. This inflation may have its most probable cause in the rapid Urbanization in India that has made unhealthy lifestyle changes (like junk food consumption, sedentary habits) mainstream. This bears major Socio-economic implications, due to which the price of anti-diabetic medications is of utmost concern now. Thus, Diabetes Mellitus has now become a cause of huge Pharmacoeconomic burden Worldwide. In most cases, customized Pharmacotherapeutic approaches have been undertaken, to tackle the complexities presented by diabetes. There have been reports of variability from person to person in risk followed by subsequent development of diabetes, along with disparities in response to various oral Glucose lowering therapies that are currently available for diabetes Pharmacotherapy. This study has been planned in order to scrutinized the patterns of prescriptions and collate the price of drugs used in DM (Type 2) in a Medical College. Prescription in a rational way specifies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period and at the lowest cost to them and their community"<sup>5</sup>. Drug utilization studies can be utilized to exhibit rational prescribing. WHO defines drug utilization as, "prescribing, dispensing, ingesting, marketing, distribution and use of drugs in society, with special emphasis on the resulting Medical, Social and Economic consequences". These data are important in order to properly examine the older drugs that are widely prescribed as well as the newer drugs in the market, analyze the wide discrepancy in the patterns of prescription and consumption of anti-diabetic medications, approach the issues of delayed adverse Drug Reactions (ADRs) and scrutinize the Inflation of drug/therapy costs<sup>6</sup>. A set of fundamental drug use indicators which will aid Health Workers to execute rational prescribing (like prescribing, patient care and health facility indicators) has been devised by the WHO<sup>7</sup>. Pharmacoeconomics is a relatively new discipline of Health Economics which helps in comparing two pharmaceutical drugs or products or therapies by estimating the expenditure and outcome in terms of effectiveness and standard of life<sup>8</sup>. These studies are a method to ensure the scientific and competent use of finite resources and the optimal functioning of wellness program in progressing nations<sup>9</sup>. The cost-effective therapy in Diabetes Mellitus serves not only the purpose of adhering to rational prescribing but also increasing the patient compliance

with lesser chances of discontinue due to pecuniary problems. This will result in fewer problems and enhance the quality of life, therefore driving therapeutic effectiveness forward significantly. Hence keeping the above observations in mind, we did this survey in patients attending Medicine outdoor of our hospital with the main focus resting on analyse of cost. Our primary aim is to study the pattern of prescriptions. Then data which was collected in a validated case report form from patients diagnosed with Type II Diabetes Mellitus. This was done in a Outpatient Department (OPD) of General Medicine and the fundamental prescribing indicators was evaluated. Information related to the cost of the drugs was obtained from College Pharmacy. Following collection, it was scrutinized and variation of percentage in the price of Anti-diabetic Drugs was calculated.

#### AIMS AND OBJECTIVES

Primary objective is to study the prescription pattern of Type II Diabetes Mellitus and its association with the degree of control of the disease.

Secondary objective is to analyze and compare the prices of different Anti-diabetic Drugs in Type II Diabetes Mellitus in a Tertiary Care Hospital.

#### MATERIALS AND METHODS

This is an observational, cross-sectional study of descriptive type. Data was collected from General Medicine Outpatient Department (OPD) of ESIPGIMSR and ESIC Medical College, Joka. Parameters studied were history of the patient, cost of therapy, drugs prescribed duration of therapy and blood for FBG, PPBG and HBA1c. These data was analyzed in the Department of Pharmacology of same institution. Patients were selected following non-probability Convenient sampling - all the patients matching the inclusion criteria during the study period were included. Seeing the previous study and duration of data collection sample size assumed to be around 300. Patients of either sex and age between 18 and 80 years came to General Medicine outdoor with a diagnosis of 'Diabetes Mellitus' according to American Diabetic Association Classification characterized by any 1 of the following criteria at least –

(a) Fasting Plasma Glucose (FPG)  $\geq 126$  mg/dl (7.0 mmol/l), also referred to as Fasting Blood Glucose (FBG), two hours postload value in the Oral Glucose Tolerance Test (OGTT)  $\geq 200$ mg/dl (11.1 mmol/l), also referred to as Postprandial Blood Glucose (PPBG), Random Plasma Glucose Level  $\geq 200$  mg/dl (11.1 mmol/l) with symptoms of Diabetes, or HbA1c levels  $>6.5\%$ .

(b) Patients excluded from the study were age less than 18 years and more than 80 years, Gestational Diabetes, Type 1 Diabetes Mellitus and patients with Major Medical Illness such as Malignancy, Autoimmune Disorder and Co-existent Neurological Disorder and Immune-compromised Disorder and Diabetic Kidney Disease.

Data was systematically entered in a Case Report Form (CRF) specifically designed for this purpose. The content validity of the questionnaire was checked by experts of qualitative research. The two-weeks test-retest reliability was checked in an initial group of 30 patients. Cronbach's alpha was used to check the reliability of the questionnaire during the initial validation. The value was found to be 0.83 and hence proved to be reliable and validated.

The case record form was designed in such a manner so as to include all demographic characteristics of the patient, disease profile, drug profile and prescription profiles. A copy of the patient's Pharmacy Bill was collected from the indoor Pharmacy for analysis. Further the drug formulation, its individual retail price, manufacturer details and the monthly cost borne by the patient will be noted down. The cost of a particular drug which is manufactured by different companies, in the same strength and dosage form were evaluated and the difference in maximum and minimum price was calculated. The Current Index of Medical Specialties and Indian Drug Review October-December, 2015 issues was used to find the Generic names, the combinations and their cost, in case the Generic names of the drugs are not written on prescription and their prices are not mentioned in the Bill.

Percentage variation in cost was calculated using this formula as follows:

Percentage cost variation

$$= \frac{\text{Cost of highest priced product} - \text{Cost of lowest priced product}}{\text{Cost of lowest priced product}} \times 100$$

Collection of data was done in a 2019 Excel file. It was summarized by routine descriptive statistics. Numerical variables would be compared between groups by Student's test, if normally distributed, or by Mann-Whitney U test, if skewed. All analyses would be 2-tailed.

Statistically significance would imply  $p < 0.05$ . Association between prescription pattern and cost was evaluated by Fischer Exact or Chi square test. The same formula was used to evaluate the association between prescription pattern and rate of control of disease. All statistical analysis was performed in R

statistical software version 3.6.1 (Language).

## OBSERVATIONS AND RESULTS

The study was performed on 55 participants and it was conducted in a period of two months.

The mean age in years was found to be 55.8 ( $\pm 10.7$ ) years. Out of 55 participants, 31 (56.4%) were females and 24 (43.6%) were males. The average duration of Type II Diabetes Mellitus in the participants was found to be 5.69 ( $\pm 3.68$ ) years (Table 1)

The number of family members is 4.98 ( $\pm 2.13$ ) on an average, while the mean per capita family income is 2662 ( $\pm 1200$ ). On the basis of BG Prasad scale, 2017, the participants were divided into classes according to their Socioeconomic status. Almost an equal number of participants from each of Lower Middle Class (18; 32.7%), Middle Class (19; 34.5%) and Upper Middle Class (18; 32.7%) were taken into consideration (Table 1).

A family history of Type II Diabetes Mellitus was present in 49.1% of the cases (27 out of 55). Adherence to anti-diabetic medication was observed in 47 participants (85.5%), while proper calorie restriction was followed by 37 participants (67.3%) (Table 2).

Table 1 — Demographic Parameters of study population

	Number (Percent) (N=55)
Age in Years Mean (SD)	55.8 (10.7)
<b>Gender :</b>	
Female	31 (56.4%)
Male	24 (43.6%)
Disease duration in Years Mean (SD)	5.69 (3.68)
Number of Family Members	4.98 (2.13)
Per capita family Income	2662 (1200)
<b>Economic Status :</b>	
Lower Middle Class	18 (32.7%)
Middle Class	19 (34.5%)
Upper Middle Class	18 (32.7%)

Table 2 — History and Biochemical Parameters of study population

	[ALL] N=55
Family history of DM :	27 (49.1%)
Adherence to medication :	47 (85.5%)
Proper calorie restriction :	37 (67.3%)
Fatigability :	33 (60.0%)
Increased thirst :	27 (49.1%)
Increased hunger :	8 (14.5%)
Frequent urination :	27 (49.1%)
Unexplained weight loss :	41 (74.5%)
Visual disturbances :	21 (38.2%)
Slow ulcer healing :	8 (14.5%)
Frequent infection :	4 (7.27%)
FBS - Mean (SD)	158 (74.5)
PPBS - Mean (SD)	241 (110)
Urea - Mean (SD)	21.4 (10.7)
Creatinine - Mean (SD)	1.01 (0.18)

33 out of the 55 participants (60%) had experienced fatigability, 27 (49.1%) felt increased thirst and only 8 (14.5%) were experiencing increased hunger, following the clinical diagnosis of Diabetes Mellitus. 27 out of the 55 participants (49.1%) were experiencing frequent urination, while unexplained weight loss had been observed in 41 cases (74.5%). 21 participants (38.2%) complained of visual disturbances. Slow ulcer healing was observed in 8 cases (14.5%), while 4 participants (7.27%) had suffered from frequent infection (Table 2).

Recent laboratory investigation reports were recorded and the mean Fasting Blood Sugar (FBS) was found to be 158 ( $\pm 74.5$ ) mg/dl, while the mean Postprandial Blood Sugar (PPBS) was 241 ( $\pm 110$ ) mg/dl. The average urea level was 21.4 ( $\pm 10.7$ ) mg/dl and the average Creatinine level was 1.01 ( $\pm 0.18$ ) mg/dl (Table 2).

Out of the 55 participants undergoing Anti-diabetic Therapy, 19 (34.54%) were found to be Normoglycemic, while the rest 36 (65.45%) were Hyperglycemic (Table 3). The total number of prescribed Anti-diabetic Medications on an average was 6.98 ( $\pm 2.41$ ), with a p-value of 0.045 (p-value  $\leq 0.05$ , proving the data is significant). In Normoglycemic patients currently on Anti-diabetic Therapy, the mean of total number of drugs is 6.16 ( $\pm 1.92$ ), while in Hyperglycemic patients currently on Anti-diabetic Therapy, it is 7.42 ( $\pm 2.55$ ) (Table 3). The mean number of drugs prescribed in Generic name was found to be 3.0 ( $\pm 2.12$ ) with p-value=0.688, while the mean number of drugs prescribed in Brand name was 4.02 ( $\pm 1.99$ ) with p-value=0.031. The average number of prescribed injectable drugs was 0.11 ( $\pm 0.31$ ) with p-value=0.012 and the mean number of prescribed Fixed Dose Combinations (FDCs) was 0.16 ( $\pm 0.42$ ) with p-value=0.005. (Table 3).

On an average, the number of prescribed anti-diabetic Drugs was found to be 2.55 ( $\pm 1.07$ ) with a p-value of 0.003 (p-value  $\leq 0.05$ , proving the data is significant). In Normoglycemic patients currently on Anti-diabetic Therapy, the mean number of Anti-diabetic Drugs is 2.0 ( $\pm 0.88$ ), while in Hyperglycemic patients currently on Anti-diabetic Therapy, it is 2.83 ( $\pm 1.06$ ). The mean number of Anti-diabetic Drugs used in clinical practice for comorbid conditions is 4.29 (2.28).

Out of 55 participants, Injectable Insulin was prescribed in the form of Inj. Human Mixtard (30/70) in 3 cases (5.45%), as Inj

Insulin Aspart + Insulin Aspart Protamine(30/70) in 1 case (1.82%) and as Inj. Insulin Degludec in 2 cases (3.64%); p-value=0.373 (Table 4).

Sulphonylureas were prescribed in the form of Glimpiride in 29 cases (52.7%) and Gliclazide in 1 case (1.82%); p-value=0.031 (p-value  $\leq 0.05$ , proving the data is significant). Biguanide like Metformin was prescribed in 53 cases (96.4%); p-value=1.0. DPP-4 inhibitors were prescribed as Sitagliptin in 11 cases (20.0%) and as Vildagliptin in 25 cases (45.5%); p-value=0.432. SGLT-2 inhibitor like Dapagliflozin was prescribed in only 1 case (3.64%) with p-value=1.0, while Thiazolidinedione like Pioglitazone was prescribed in 4 cases (7.27%), with p-value=1.0. Alpha-Glucosidase inhibitor like Voglibose was prescribed in 9 cases (16.4%); p-value=0.141 (Table 4).

It was found that the total number of drugs prescribed was higher in presently Hyperglycemic patients under anti-diabetic Therapy compared to presently Normoglycemic patients under Anti-diabetic Therapy (Fig 1).

The total cost of treatment was 13182 ( $\pm 9094$ ) on an average and was subsequently found to be higher in presently Hyperglycemic patients under Anti-diabetic Therapy (14547 $\pm$ 9144) than in presently Normoglycemic patients under Anti-diabetic therapy (10595  $\pm$ 8646); p-value=0.122 (Fig 2).

A weak positive correlation was found between family income per capita and total cost of treatment with Pearson's correlation coefficient, r=0.145; p-value=0.287 (Fig 3).

## DISCUSSION

Diabetes Mellitus (DM) is a disease which results in severe complications in long-standing cases and is currently deemed as a Global epidemic by WHO. It requires Multiple Drug Therapy and may be associated with various other comorbidities, especially in the elderly age group. This may lead to adverse drug reactions and drug-drug interactions and in turn increases the risk of Social, Clinical as well as Financial burden. The patient compliance depends

Table 3 — Pattern of drug prescription in presently Normoglycemic and Hyperglycemic individuals. Unpaired t-test was used to calculate p-values. Significance level was 0.05

	[ALL] Mean (SD) N=55	Normoglycemic Mean (SD) N=19	Hyperglycemic Mean (SD) N=36	p-value
Total Number of Drugs	6.98 (2.41)	6.16 (1.92)	7.42 (2.55)	0.045
Drugs prescribed in Generic name	3.00 (2.12)	2.84 (2.06)	3.08 (2.17)	0.688
Drugs prescribed in Brand name	4.02 (1.99)	3.32 (1.42)	4.39 (2.16)	0.031
Injectable drug prescribed	0.11 (0.31)	0.00 (0.00)	0.17 (0.38)	0.012
Fixed Dose Combination prescribed	0.16 (0.42)	0.00 (0.00)	0.25 (0.50)	0.005
Anti-diabetic Drugs Prescribed	2.55 (1.07)	2.00 (0.88)	2.83 (1.06)	0.003
Drugs Prescribed for comorbid condition	4.29 (2.28)	4.00 (1.63)	4.44 (2.57)	0.438



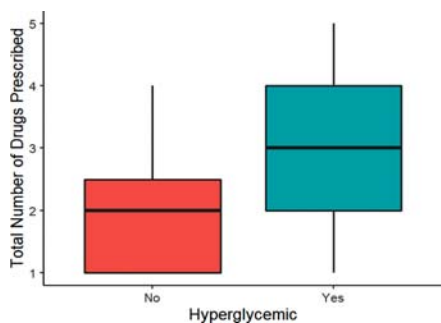


Fig 1 — Number of Drugs prescribed is higher in presently hyperglycemic patients

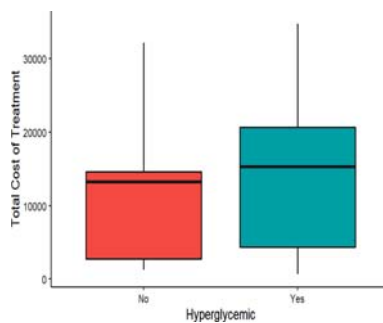


Fig 2 — Cost of treatment is higher in presently hyperglycemic patients

Table 4 — Drug Utilization Pattern in presently Normoglycemic and Hyperglycemic individuals. Chi-squared Test with Yates' correction was used to calculate p-values. Significance level was 0.05

	[ALL] N=55	Normoglycemic N=19	Hyperglycemic N=36	P overall
Insulin : Not Prescribed	49 (89.1%)	19 (100%)	30 (83.3%)	0.373
Inj. Human Mixtard	(30/70)	3 (5.45%)	0 (0.00%)	3 (8.33%)
Inj. Insulin Aspart + Insulin Aspart Protamine	(30/70)	1 (1.82%)	0 (0.00%)	1 (2.78%)
Inj. Insulin Degludec	2 (3.64%)	0 (0.00%)	2 (5.56%)	0.031
Sulphonylurea : Not Prescribed	25 (45.5%)	12 (33.3%)	13 (68.4%)	
Gliclazide	1 (1.82%)	0 (0.00%)	1 (2.78%)	
Glimepiride	29 (52.7%)	6 (31.6%)	23 (63.9%)	1.000
Biguanides: Not Prescribed	2 (3.64%)	1 (5.26%)	1 (2.78%)	
Metformin	53 (96.4%)	18 (94.7%)	35 (97.2%)	
DPP4 Inhibitor : Not Prescribed	19 (34.5%)	8 (42.1%)	11 (30.6%)	0.432
Sitagliptin	11 (20.0%)	2 (10.5%)	9 (25.0%)	
Vildagliptin	25 (45.5%)	9 (47.4%)	16 (44.4%)	
SGLT2.Inhibitor : Not Prescribed	53 (96.4%)	18 (94.7%)	35 (97.2%)	1.000
Dapagliflozin	2 (3.64%)	1 (5.26%)	1 (2.78%)	
Thiazolidinediones: Not Prescribed	51 (92.7%)	18 (94.7%)	33 (91.7%)	1.000
Pioglitazone	4 (7.27%)	1 (5.26%)	3 (8.33%)	
AG Inhibitor : Not Prescribe	46 (83.6%)	18 (94.7%)	28 (77.8%)	0.141
Voglibose	9 (16.4%)	1 (5.26%)	8 (22.2%)	

Type 2 DM. Different Databases were searched for drawing conclusion from the result obtained, The important one states that, stringent control of Blood Pressure is considerably more cost-effective than less strict control. This was described in 6 studies<sup>13</sup>. In another systematic review, clinical effectiveness and cost-effectiveness of two drugs rosiglitazone and pioglitazone in the treatment of DM (Type II) was compared<sup>14</sup>, whereas in another study, safety, effectiveness and cost of DPP-4 inhibitors were compared with intermediate acting Insulin for DM (Type II)<sup>15</sup>. The prescriptions of 55 Diabetic Patients were collected and scrutinized. Demographic analysis shows that the mean age of the participants was 55.8 years with a range between 34 and 72 years, which is congruous with the demographic findings of the study by Acharya *et al*<sup>16</sup>. This indicates a preponderance of Type II Diabetes Mellitus in middle-aged individuals, which may have a significant negative influence on quality of life. A higher percentage of females (56.4%) as compared to males (43.6%) was observed in our study

largely on the expenditure component in Anti-diabetic Therapy and it is important that clinicians ponder wisely while choosing the Anti-diabetic Drugs (be it in brand names or Generic names) in order to alleviate the Pharmaco-economic burden and improve the health status of the patient<sup>10</sup>. As a result, we have conducted this study to know the prescription patterns of drugs commonly used for the treatment of Type II Diabetes Mellitus and subsequently analyze the total cost burden on diabetic patients. The Hyperglycemia observed in diabetes may be followed by chronic complications like dysfunction and ultimately failure of different organs, especially Kidneys, Blood Vessels, Heart, Eyes and Nerves. In fact, the development of Diabetes Mellitus involves numerous pathophysiological events<sup>11</sup>. Diabetes Mellitus (DM) is a common and serious disease in America but one third of those affected are unaware they have it<sup>12</sup>. A systematic review was projected to give an outline of the pecuniary evaluations of preventive measures in

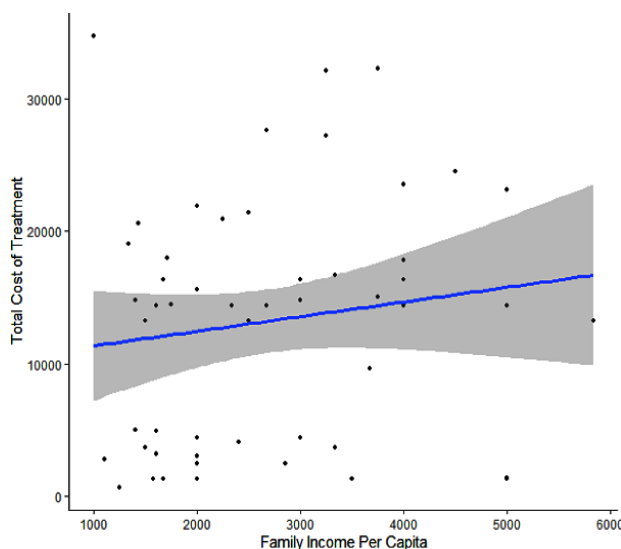


Fig 3 — Family income per capita has weak positive correlation with total cost of treatment (Pearson's r = 0.145, p-value = 0.287)

as opposed to the study by Abdi *et al*<sup>17</sup>. The average duration of Type II Diabetes Mellitus in the participants was found to be 5.69 ( $\pm 3.68$ ) years which is much less compared to the findings in the study by de Pablo-Velasco *et al*<sup>18</sup>. These disparities may be due to the limited sample size and shorter duration of the study. 49.1% of the participants (27 out of 55) presented with a family history of Type II Diabetes Mellitus, meaning either one or both of their parents suffered from the same. This in contrast to the findings of Kannan *et al*, where the majority of Diabetic Patients showed Genetic preponderance<sup>19</sup>. However, it is in consistency with the low prevalence of Genetic Preponderance as found by Assefa *et al*<sup>20</sup>. Recent laboratory investigations showed that 65.45% (36 out of 55) participants were hyperglycemic, with the mean FBS levels being 158 ( $\pm 74.5$ ) mg/dl. This is in accordance with the findings of Assefa *et al*<sup>20</sup>. In our study, the total number of medications used in clinical practice on an average was found to be 6.98 ( $\pm 2.41$ ), while the number of prescribed Anti-diabetic Drugs was 2.55 ( $\pm 1.07$ ). This is a relatively high number, which indicates the trend of polypharmacy in treatment of Type II Diabetes Mellitus. Furthermore it was found that a relatively higher frequency of drugs were being prescribed as brand names (mean of 4.02), as compared to prescription of drugs in Generic names (mean of 3.0). This indicates a tendency of Pharmaceutical Companies to influence prescription patterns of Anti-diabetic Drugs. On the other hand, this may also be an effort on the part of the Physician to maintain standard quality of drug composition, to prevent Pharmacies from selling only specific brands which provide higher profit margins. The preferred route of Drug Administration was found to be oral in 49 cases (89.09%) with injectable insulin prescribed in only 6 participants (10.9%) which is in agreement with the study by Abidi *et al*<sup>10</sup>. This is assumably due to the fact that the study was performed in OPD conditions and injectable Insulin was prescribed only when the Blood Glucose parameters were not well controlled by oral anti-diabetic drugs. Biguanide, that is, Metformin was the most frequent Anti-diabetic Drug to be used in clinical practice (53 participants, 96.4%), followed by DPP-4 inhibitors like Sitagliptin and Vildagliptin in 36 cases (65.45%) and Sulphonylureas like Glimepiride and Gliclazide in 30 cases (54.54%). This conforms to the findings of Acharya *et al*<sup>16</sup>. However it is in complete contrast to the study by Abdi *et al* which is conducted during hospital stay of the patients<sup>17</sup>. The total cost of treatment was significantly higher in presently hyperglycemic patients

under Anti-diabetic Therapy compared to their Normoglycemic counterparts. This is in par with the finding in our study that the total number of medications advised in presently Hyperglycemic patients exceeds the number prescribed in presently Normoglycemic patients. This may also be due to the requirement of additional drugs for associated comorbidities or complications, which may manifest earlier in case of poorly controlled Type II Diabetes Mellitus. Furthermore in our study, the total cost of treatment and per capita family income are found to be positively correlated, but the Pearson's correlation coefficient was relatively low ( $r=0.145$ ). This suggests that the total cost of treatment remains limited to a specific range ( $13182 \pm 9094$ ) irrespective of the Socioeconomic status of the patient. This may indicate increased Economic burden on the patients from lower and lower middle Socioeconomic classes. It may be presumed that better prescription practices by prescribing drugs with the knowledge of market drug prices would significantly eliminate this problem. A study by Frazier *et al* shows that patients' drug expenditure can be reduced by providing a manual of comparative drug prices annotated with prescribing advice to Physicians<sup>21</sup>.

### CONCLUSIONS

In our study, the number of Hyperglycemic patients far exceeded the number of Normoglycemic patients, despite both groups being under anti-diabetic therapy. As a result, the average tally of Anti-diabetic Medications prescribed in Hyperglycemic patients is higher as compared to their Normoglycemic counterparts. The most common Anti-diabetic Drug used in clinical practice is Metformin, followed by DPP-4 inhibitors and Sulphonylureas and the most preferable route of drug administration is oral route in the prescriptions analyzed in our study. The total cost of treatment in presently Hyperglycemic patients under Anti-diabetic Therapy was significantly high, though the average total cost was limited to a specific high range for all included Socioeconomic classes. In most of the patients, the monthly expenses due to Anti-diabetic Therapy is significantly high, which increases the Economic burden of those belonging to lower Socioeconomic classes. Thus, a need for rational prescribing as well as Physician knowledge of current drug prices is felt, to ensure patient compliance. The conduction of this study was faced with multiple limitations like the COVID-19 pandemic which delayed the study process and also decreased OPD Department influx in the hospital (converted to a COVID-19 center during the pandemic) where the study was

carried out. As a result, the sample size is relatively small, which may increase errors. This study could be improved by increasing the sample size and also conducting the study over a longer duration of time.

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## Original Article

### COVID and Women's Health in India

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**Background :** COVID-19 disease surfaced in Wuhan in December, 2019 and rapidly spread in the World as a pandemic (March, 2020) Till date (10 August) COVID-19 has affected 20 million people. Many women have delivered and many conceived during this time. Till date very few adverse effects and vertical transmission is observed. WHO later changed the terminology to SARS-COV-2 and removed '19' from the name.

**Material and Method :** We studied Maternal and Perinatal outcome of COVID confirmed pregnancies and the effects of CORONA infections on Women's Health.

**Results :** Most of the patients were asymptomatic. Majority 80% cases of our cases were delivered by Cesarean Section. Cesarean Section was done for Obstetric reasons along with early consideration due to COVID concerns. Meconium Stained Liquor and Fetal Distress was the indication of Cesarean in 14% cases. Previous Cesarean Sections was a major cause of repeat cesarean in our study. Preterm labour was reported in only one case of Twin Pregnancies. Premature Rupture of Membranes was not seen in any of the pregnancies. Maternal and Fetal outcome were favorable with only few cases of mild to moderate Pneumonia in mothers.

Most of the women were psychological disturbed due to the Lockdown and had unwanted pregnancy (due to lack of contraceptive availability), domestic violence and also family disputes and child beating were reported by many in the survey. Due to lack of Medical Services by the GP's and the friendly small Obstetrics Gynaecology clinics (closed due to Lockdown) small problems got aggravated and a lot of these women one now coming up with Anemia, Polycystic Ovarian Syndrome (PCOS), Fibroids, Abnormal Uterine Bleeding (AUB), Endometriosis, Pelvic Inflammatory Disease (PID), Cervical Croisers, Vaginitis, Obesity etc.

**Conclusion :** Coronavirus infection in pregnancy did not adversely affect the pregnancy and has a benign course. Pregnant women are not at higher risk of developing Pneumonia compared to non pregnant women. There is no evidence of increased risk of miscarriage or foetal losses with COVID-19 infection during pregnancy. But SARS-COV-2 disease a lot of other Gynaecological problems and adversely affected Women's Health.

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**Key words :** COVID- 19, Pregnancy Perinatal Outcome, Vertical transmission, Maternal outcome, Pregnancy Outcome, Corona virus, COVID-19 pandemic.

Since the declaration of COVID-19 as a pandemic on March 13<sup>th</sup> 2020 and renaming the disease as SARS-COV-2 by WHO, the World Health Situation has been adversely affected over 218 countries are still reeling under the Corona Virus attack (as of July, 31<sup>st</sup>)<sup>1</sup>.

On December, 2020 the world is facing the second & Third wave and Lockdown again.

A total of 69.6 million (December 1<sup>st</sup>) World population has been affected and the virus is killing people in huge numbers. The death count stands at 1.58 million (December 1<sup>st</sup>)<sup>2</sup>.

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#### Editor's Comment :

- Even through pregnancy is a state of reduced immunity of the women, COVID infections are being seen as mild in pregnancy during the first wave. SARS-COV-2 disease can produce serious problems in Mother & Fetus, hence it is necessary for all pregnant & lactating women to get vaccinated & to follow COVID appropriate behaviour.

The pandemic has hit Women's Health ever more severely unwanted pregnancies are estimated to be in millions. About 4.5 million abortions could not be done in India due to Lockdown and routine OPDs being shut, sterilization services halted and normal hospitals being converted to dedicated COVID centres to be prepared for the pandemic. Millions have given births during the pandemic. It is expected that due to lack of reproductive services in the last 5 months, the number of births will be 24.1 million from January to December, 2020. According to UNICEF India & China will face largest burden of pandemic pregnancies and births, 20.1 million expected in India<sup>3</sup> and also various other



Women’s Health problems (Gynaecological problems).

**MATERIAL AND METHOD**

A survey was done on all women attending OPD in the Lockdown pandemic period and in Unlock period.

Gynaecological patients were divided in AUB, Unwanted pregnancy, Incomplete / Ectopic pregnancy, Psychological problems, Domestic violence. We wish to state that descriptive statistics have been used in our study as percentage.

**RESULTS**

**Obstetrics :**

From 15th March to 1st December we had 135 Corona virus RT-PCR confirmed cases of which mean age of the patients was 27.2 years, majority of patients (90%) had no symptoms, rest had only mild illness (low grade fever, cough and sore throat). They did not develop symptoms during the course of their stay in hospital. Ninety percent patients were more than 32 weeks gestation at presentation.

Many patients come in advanced labour where waiting for the RTPCR test report was not possible and these were triaged and delivered after a Rapid Antigen testing.

**Gynaecology :**

**Maternal Outcome :**

Only 10 patients presented at first trimester, First was a case of twin pregnancy conceived as a result of in-vitro fertilization but landed in Missed abortion at 12 weeks but her abortion could not be clearly attributed to COVID -19 because she was already at high risk of abortion, but her further testing of causes of abortion could not be done.

Two cases were first trimester ruptured Ectopic Pregnancies for which Laparoscopy and Salpingectomy was done. Three pregnancies reported in second trimester were at 16 weeks and other at 24 weeks with Cholecystitis Maternal Comorbidities like Gestational Diabetes and Hypothyroidism were present in only 1-2% cases. Pre-eclampsia was reported in 8% cases

Intrauterine Fetal death was reported in 2 cases, one presented at 32 weeks and other at term with Fetal Distress. Only 3 patients had moderate Pneumonia on CT and they recovered. One patient had severe Pneumonia and recovered on BiPap. One case of Vaginal delivery with only mild fever was discharged in healthy condition but she expired on the way to hospital on 5<sup>th</sup> day of delivery. her sample

report was awaited at the time of discharge. One more Maternal Mortality was reported in our cases. Maternal outcome was overall favourable as infection acquired at term was not likely to cause adverse Fetal outcome and our cases were mostly near term.

Fetal Outcome		Total births (n=135)
Fetal Complications	IUGR	3 (2.1%)
	Thick Meconium stained Liquor	21 (14.9%)
	Still Born	3 (2.1%)
Mean Apgar score (1 minute)		8 ± 1
Mean Apgar score (5 minutes)		9 ± 1
Mean Birth weight (g)		2800 ± 386 gram
SARS-CoV-2 infection in Neonate Tested by RT- PCR 36- 48 hours after delivery		0
Perinatal complications	Premature delivery	3 (2.1%)
	Low birth weight (<2500 g)	8 (6.3%)
	Live birth	132 (97.9%)
	Severe neonatal asphyxia	5(3.7%)
	Neonatal intensive care unit admission	6 (4.2%)
	Neonatal death	2(1.5%)

**Mode of Delivery:**

Majority 80% cases were delivered by Cesarean Section. Cesarean Section was done for Obstetric reasons along with early consideration due to COVID concerns. Meconium stained liquor and Fetal distress was the indication of Cesarean in 14% cases. Previous Cesarean sections were a major cause of repeat Cesarean in our study. Preterm labour was reported in only one case of Twin pregnancies. Premature Rupture of membranes was not seen in any of the pregnancies.

**Gynaecology Outcomes :**

**Treatment Prescribed :**

We did not prescribe antiviral drugs, *none of these patients received Remdesivir, Ticloziber or Plasma Therapy till August.* After August the patients were given Remdesivir and seriously ill patients were transferred to COVID Hospitals.

Routine steroids or Hydroxy chloroquine were not prescribed to patients. Antibiotics were prescribed to all patients. It took approximately 9 days for RT-PCR to become negative in all patients. All Cesarean Sections were done in Spinal anaesthesia.

**Labour Room Management :**

Continuous Fetal Heart rate monitoring was done. All staffs were donned in proper personal protective equipments. Active management of third stage was done in all cases. 2 cases had Postpartum Hemorrhage, one was given condom Catheter (ballon

tamponade) which was removed 48 hours after delivery and other case was given compression sutures at the time of cesarean section.

#### **Postpartum Management :**

Postpartum baby as separated from the mother till mothers COVID-19 RT-PCR was negative. Breast feeding was allowed after mothers report was negative. One baby who breast fed as mothers COVID status was not known was confirm RT-PCR positive, rest all babies (100%) were negative for COVID-19, test being done 48 hours after delivery. We also examined Amniotic Fluid and Breast Milk in 3 cases and they had no evidence of Coronavirus infection.

#### **Neonatal Outcome :**

Apgar score was good in all Neonates except 2 cases of Neonatal Asphyxia, which were shifted to Neonatal ICU. We found that Fetal Affection in the last trimester did not affect baby weight or growth. Intrauterine Growth Restriction (IUGR) was present in cases with associated Preeclampsia

#### **DISCUSSION**

Pandemic pregnancies are not only facing lack of Antenatal care, Intranatal care, Postnatal care but a Major problem of Psychological Stress<sup>4</sup>.

Maternal stress has been linked with neurodevelopmental disorders in babies. Anxiety and depression have been moderately increased in pregnant women in India. Babies born are likely to be at risk of Neuro developmental problems, Attention deficit Hyperactive Disorder and Autism. More preterm, growth retarded and medically disorder complicated pregnancy and births are likely to happen<sup>4</sup>.

Although pregnancy is an immune compromised state and pregnant women are at an increased risk of acquiring viral infections like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Till now there has been no documented evidence that pregnant women are at increased risk of acquiring COVID-19 than general population. We also reached to the same conclusion. Similarly, apart from one or two case reports, there is no evidence that COVID-19 has vertical transmission<sup>4</sup>. Most of the Placentas, Amniotic fluid, Cord blood and Blood and Respiratory samples of Neonates born to COVID-19 positive mothers, have been found to be negative. SARS and MERS caused adverse Obstetric outcome during pregnancy with higher Maternal Morbidity and Mortality, vertical transmission of virus and increased risk of miscarriages, Perinatal Infections and Perinatal Mortality<sup>5,6</sup>. No such adverse impact of COVID-19 has been observed during Gestation. This

is currently a priority for research and the data is at an evolving stage. It will take several years to completely understand the implications for babies born in the COVID-19 pandemic. Pregnant women being young may not develop Dyspnoea or other symptoms till late disease and then suddenly may collapse with very advanced disease. Use of Pulse Oximetry may be of use to detect severe disease in early stages.

Schwartz analysed 38 pregnant women with COVID-19, their newborn infants and Maternal-foetal Transmission from China and reported no maternal death, no intrauterine transmission of COVID-19 from mother to their foetuses with all Neonatal Specimens and breast milk tested being negative for the virus<sup>5</sup>.

There is no evidence of risk of miscarriage or foetal losses with COVID-19 infection during Gestation. As per studies available till date, COVID-19 is not teratogenic and COVID-19 infection during pregnancy doesn't warrant Medical termination of pregnancy. Although, there were some case reports of premature labour, Preterm Prelabour Rupture of Membranes (PPROM) and Foetal compromise, most other studies reported normal outcome. Also, Preterm labour can be iatrogenic or due to poor Maternal condition in some cases<sup>8-11</sup>.

#### **Should We Routinely Screen All Women Attending Antenatal Clinics :**

A study by Sutton in The New England Journal of Medicine analyzed data from pregnant women who delivered in New York City and reported that out of 215 patients, 88% of women who tested positive for COVID-19 did not show any symptoms. By routine screening of asymptomatic women by Breslin *et al* and D Sutton *et al* 13.7% COVID positive pregnant women were found<sup>13,14</sup>.

Routine screening of all women is not cost effective and is not recommended in India in the current scenario. There is risk of failure of Healthcare system if COVID-19 cases rise putting burden on hospitals and staff. We should judiciously use the limited resources for best possible outcome. Capanna *et al* "from their experiences in Europe at the peak of COVID-19 pandemic have recommended preparation of an Obstetric unit with quick reorganization<sup>15</sup>.

Available literature does not support that Coronavirus crosses the Placenta and infects the Fetus; few cases of in Utero infection have been reported. Most studies of Amniotic fluid, Cord blood, Vaginal secretions and Breast milk did not find vertical transmission. A meta-analysis was published by Mascio *et al* in the American Journal of Obstetrics and Gynaecology MFM<sup>16</sup> in which 41 COVID positive

Pregnant Women were studied and the following complications were noted:

Preterm birth <37 weeks (41.1%), PPRM (18.8%), Preeclampsia (13.6 %) and Caesarean delivery (91.1 %). Emerging evidence now suggests that vertical transmission is probable, although the proportion of pregnancies affected and the significance to the neonate is yet to be determined.

Chen *et al* and others have found no evidence of COVID-19 in the Amniotic Fluid or cord blood of infants of infected women<sup>17</sup>. At present, there are no recorded cases of vaginal secretions being tested positive for COVID-19. Liu *et al* didn't find any aggravation of symptoms or CT features of COVID-19 Pneumonia in their study on pregnancy and Perinatal outcome in COVID-19 Pneumonia patients<sup>18</sup>.

Evidence from China suggests that the virus may be transmitted vertically (from mother to the baby from the Placenta Babies all born by C-section, to COVID positive mothers, tested positive for Coronavirus. At present, there are no recorded cases of breast milk being tested positive for COVID-19<sup>19,20</sup>.

There are currently no data suggesting an increased risk of miscarriage or early pregnancy loss in relation to COVID-19 nor evidence that the virus is Teratogenic. Long term data is awaited.

COVID-19 infection is currently not an indication for Medical Termination of Pregnancy.

A report concluded that only 8% had what the WHO classified as "Severe Disease" and 1% were "Critical"<sup>18-20</sup>.

It was determined that they weren't more likely than Non-pregnant people to develop a life-threatening illness.

A study of pregnant women with confirmed COVID-19 found that unlike SARS and H1N1, pregnant women do not seem to experience more severe illness from the Coronavirus compared to the general population<sup>20</sup>.

They warn that the data reflect small numbers and more studies are required.

All results may change with availability of more data from the World as scenario is changing each day. However, women with comorbidities especially congenital and acquired heart disease are more at risk of getting the viral disease and are at increased risk of serious disease like COVID Pneumonia. They should be particularly taken care of by the attending Obstetricians for Optimum Outcome and timely transfer to Intensive Care Unit (ICU) in case of need for the same.

COVID disease has increased the problems of providing proper reproductive care to our women. A

surge of unwanted pregnancy, self medication for abortions and MTP's has been noted all over the Country.

This problem of lack of care & fear is likely to persist for a year (Post COVID years).

A new strategy must be quickly put into place to ensure women don't die and women are not denied of the essential reproductive services (Contraception, MTP, Gynaecological disease evaluation, Surgery, Infertility treatments and Safe pregnancy and safe delivery and post partum care).

#### Limitations :

The study was carried out in the First wave of COVID infection as an observational study and there was not enough data to support.

#### Conclusion :

Covid (SARS-COV-2) (Coronavirus) is here to stay for long time.

Our observations indicate, if we give proper care we can manage most of the COVID-19 pregnancies safely in the First wave. COVID-19 did not alter the course of pregnancy in late third trimester. Neonatal outcome is also not affected but it can cause serious concerns in Mother and Fetus according to statistics of Second wave. It is important for all to follow COVID appropriate behaviour and get vaccinated.

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## Review Article

# Bladder Innervation and Types of Neurogenic Bladder

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Bladder innervation is a complex network integrating the activation of Autonomic Nervous System and somatic Nervous System controlled by Central Nervous System. Due to the intricacies of the Neural mechanisms involved, this whole process of Bladder control and Micturition is subject to varied pathological insults at various levels. Neurogenic Bladder is classified depending on the location of the lesion. Only a clear understanding of these mechanisms will allow us to obtain a detailed history and thus initiate appropriate treatment strategies. This review highlights the Anatomy and Physiology of various Neural Networks regulating the Bladder function and also the varied manifestations of Neurogenic Bladder, which will guide us in successful therapeutic interventions.

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**Key words :** Bladder Innervation, Neurogenic Bladder, Micturition center

### Bladder Innervation :

The Central Nervous System (CNS) plays a major role in coordinating the activation of Autonomic Nervous System (ANS) with the Somatic Nervous System (SNS) in the process of micturition. The Lower Urinary Tract comprising of Bladder and Urethra is innervated by the Sympathetic, Parasympathetic and SNS; which contain both afferent sensory and efferent motor axons.

Parasympathetic preganglionic innervation to Lower Urinary Tract arises from the sacral parasympathetic or Detrusor nucleus located in the lateral part of sacral intermediate gray matter at S2-S4 cord level (spinal micturition centre)<sup>1</sup>. These Preganglionic Parasympathetic Neurons travel through the Pelvic Nerves to reach the peripheral ganglia in the Pelvic Plexus and Detrusor wall layer. Parasympathetic Postganglionic Nerve terminals induce Detrusor contraction by releasing acetylcholine. Nitric Oxide is released and Detrusor contraction and Proximal Urethral Relaxation occurs as a consequence of the activation of the Sacral Parasympathetic Outflow.

Sympathetic preganglionic outflow from T11 to L2 cord level travel through the inferior mesenteric and hypogastric plexuses and via the Hypogastric Nerves to innervate the  $\alpha$ -adrenergic receptors in proximal Urethra and the Bladder neck. Sympathetic Nerve fibers also innervate and have an inhibitory effect on Parasympathetic Ganglia in the Detrusor wall.

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### Editor's Comment :

■ Understanding Bladder Anatomy and Physiology will help us in localisation of various Neurological Diseases. A thorough knowledge of the various types of Neurogenic Bladder is essential for clinical reasoning, diagnosis and therapy.

Activation of the Thoracolumbar Sympathetic Outflow results in Detrusor relaxation and Bladder neck (internal sphincter) contraction mediated by the release of norepinephrine at their postganglionic terminals.

The external Urethral Striated Sphincter Muscle is innervated by Pudendal Nerve which receives its somatic efferents from Pudendal Nucleus (Onuf's nucleus)<sup>2</sup> at the S2-S4 cord level. Activation of Pudendal Nucleus which is under the voluntary control of supraspinal centers, results in sphincter muscle contraction through the release of acetyl choline which acts on Nicotinic receptors.

Afferent sensory information from the Bladder is conveyed through sensory fibres in the suburothelial and muscular plexuses to Lumbosacral Spinal Cord through Pelvic, Hypogastric and Pudendal Nerves<sup>3</sup>. The pelvic sensory afferents predominantly consist of small myelinated A $\delta$  fibers and unmyelinated C fibers which respond to bladder wall distension and painful stimuli respectively.

Supraspinal input influences the voluntary control of micturition, which is needed to preserve continence and to postpone Bladder emptying until an appropriate time and place to void are chosen. Most afferent fibers do not just terminate in the sacral levels of the Spinal Cord but ascend further to synapse on relay cells located in the dorsal Pontine Micturition Center (PMC or Barrington's nucleus). PMC is located in the locus ceruleus, pontomesencephalic gray matter and nucleus tegmentolateralis dorsalis. It is vital for the process of

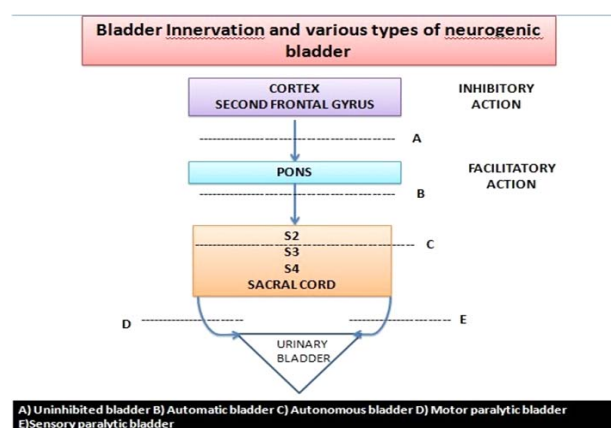
micturition by coordinating the antagonizing effects of the Sympathetic and Parasympathetic Nervous Systems on the Urinary Tract. The subcortical centers are located in multiple sites including Thalamic Nuclei, Subthalamic Nuclei, Limbic System, Substantia Nigra, Hypothalamus and the Red Nucleus.

The Filling Phase and the Emptying Phase are the two phases occurring in a normal Urinary Bladder. To maintain urinary continence, they both work together as a coordinated unit to store and empty urine. An increase in Bladder pressure due to raised intra abdominal pressure is counteracted by a rise in urethral pressure.

During storage phase, there is a passive low pressure filling of Bladder while the urinary sphincter maintains high resistance to the urine flow. Whereas during the emptying phase, there is Detrusor contraction to void urine along with relaxation of external and internal urinary sphincter which allows un-interrupted urinary outflow. The Neural Circuits in Brain and Spinal Cord coordinates this whole process of micturition by acting as on-off switches (phasic patterns of activity) to alternate the lower Urinary Tract between storage and voiding of urine<sup>4</sup>. Micturition process is under voluntary control and it depends on a learned behaviour<sup>5</sup>.

During the filling phase, the Detrusor is inhibited and the Urethral sphincter is contracted to prevent involuntary emptying of Bladder via the activation of parasympathetic outflow. This whole process is organized by a group of urethral reflexes termed as guarding reflex, which are activated by Bladder afferent activity relayed through the Pelvic Nerves, and organized further by interneuronal circuitry located in the Spinal Cord. During the filling phase, supraspinal centres inhibit the pontine micturition center resulting in an enhanced thoracolumbar sympathetic outflow along with parallel suppression of sacral parasympathetic supply to the Lower Urinary Tract. In addition, supraspinal centers also send excitatory signals to external urethral sphincter via the Pudendal Nerve resulting in sphincter contraction.

During the voiding phase of Bladder, inhibitory effect of supraspinal centers on the pontine micturition center is suppressed. The PMC gets activated and conveys its inhibitory influence to Thoracic sympathetic outflow along with an enhanced sacral parasympathetic outflow to the Lower Urinary Tract. The excitatory output of supraspinal centers through the Pudendal Nerve is also suppressed, producing external urethral sphincter relaxation. Net effect is detrusor smooth muscle contraction, Bladder Neck smooth muscle relaxation, and external Urinary Sphincter Skeletal Muscle



relaxation allowing evacuation of stored urine from the Bladder.

Though micturition reflex is essentially the basis of micturition process, the voluntary or conscious control of urination is controlled by supraspinal centers. Afferent sensory information to the Anterior Cingulate Cortex, Prefrontal Cortex and Insula send inhibitory action on the PAG, whereas the Hypothalamus has an excitatory action on it. Whenever a conscious decision to void is made, there occurs an interruption of prefrontal Cortex's inhibitory influence on the PAG and a simultaneous hypothalamic stimulation of the PAG. This finally leads to excitation of the PMC (due to the excitatory input from PAG) thereby voiding takes place.

Thus, a person voluntarily contracts the abdominal muscles during the initiation of Voluntary Urination, thereby Bladder pressure is increased. The stimulation of stretch receptors results in generation of the Micturition Reflex<sup>6</sup>.

#### Types of Neurogenic Bladder :

- An uninhibited type of Neurogenic Bladder Dysfunction occurs with Supra Pontine Neurologic Lesions, in which there is loss of tonic inhibition of pontine micturition center due to cortical or subcortical structural damage. With such Brain Lesions above PMC, particularly with Bilateral Lesions, there is a reduced perception of Bladder fullness and a low capacity Bladder resulting in urinary incontinence<sup>7</sup>. Since the PMC here is intact, the normal oppository effect of Detrusor and internal or external sphincter tone is maintained. So there is no increase in bladder pressure that can lead to upper Urinary Tract Damage. This type of uninhibited Neurogenic Bladder can be seen with various suprapontine Cortical Lesions including Stroke, Parkinson's disease, Brain tumor and Shy-Drager syndrome. Even though Cerebrovascular accidents are usually associated with urge incontinence and Detrusor overactivity, some

cases of Detrusor Underactivity have also been reported.

- An upper Motor Neuron type of Automatic Bladder or Hyperreflexic Neurogenic (spastic) Bladder occurs with Spinal Cord Lesions above the level of the sacral micturition center and below the level of the pontine micturition center (associated usually with either paraplegia or quadriplegia). A Detrusor overactivity is seen. Loss of the normal inhibition from higher centers results in Detrusor contractions during Bladder filling. Damage to the Spinal Cord causes the Bladder and Sphincters to become spastic and the Bladder capacity is very much reduced, especially if lesions are above the T10 level (above the sympathetic innervation of the Bladder). There can also be a development of characteristic Detrusor Sphincter Dyssynergia (DSD), wherein simultaneous Detrusor and Urinary Sphincter contractions cause high Bladder pressures of up to 80-90 cm H<sub>2</sub>O leading to vesicoureteral reflux that can lead to Renal Failure<sup>8</sup>. All this culminate in incomplete emptying. In majority of cases, urinary urgency, urinary frequency, urge urinary incontinence, and intermittent stream or hesitancy is seen. Even small volumes of urine tend to stimulate Detrusor contraction; the Bladder capacity is reduced but the residual urinary volume may be increased (increased post micturition residual volume). Here, the anal and bulbocavernous reflexes usually are preserved.

- An autonomous type of Neurogenic Bladder (Detrusor Areflexia) can be seen with complete cord lesions below the T12 segment involving the Sacral Spinal Cord. This type of Bladder dysfunction can occur with sacral myelomeningocele or sacral level cord injury and also with Conus Medullaris or Cauda Equina Region Tumors. Features suggestive of Autonomic Bladder Dysfunction also occur during the phase of spinal shock following cord injury. There is a weak or absent detrusor contraction (Detrusor underactivity or areflexic/ acontractile Detrusor) and a tonic contraction of the smooth urinary sphincter (non-relaxing urethral sphincter obstruction). The Bladder is paralyzed and sensation of bladder is lost. This results in urinary retention. Ultimately there can be a difficulty in initiation of micturition, overflow incontinence and also elevated residual urinary volume. Patients develop associated saddle anaesthesia with absent superficial anal and bulbocavernous reflexes.

- A sensory Paralytic (de-afferented) Bladder may occur in tabes Dorsalis, Syringomyelia or Diabetes Mellitus. It is caused by the impairment of the afferent pathways to the Bladder or by the damage of the

posterior columns or Lateral Spinothalamic Tract at the spinal cord level resulting in prevention of transmission of stretch signals from Bladder. Early symptoms can be retention of Urine or overflow incontinence or a Urinary tract infection. In syphilis, Constrictive fibrosis around the Dorsal nerve fibers destroys them leading to a bladder condition named as Tabetic Bladder.

- A Motor Paralytic (de-efferented) Bladder occurs when the lesions involve the efferent motor fibers to the Detrusor or the Detrusor Motor Neurons in the Sacral Spinal Cord for example Lumbar Spinal Stenosis, Lumbosacral Meningomyelocele, or following Radical Hysterectomy or Abdominoperineal Resection. These patients primarily suffer from painful urinary retention or impaired Bladder emptying with markedly elevated residual urine volume. There is sparing of sacral and bladder sensations, but the anal and bulbocavernous reflexes usually are absent.

#### Conclusion :

Normal micturition is controlled by Neural Circuits in the Brain and Spinal Cord modulating the activity of smooth muscles in the Bladder and Urethra. Due to the complexity of Neural Networks regulating the Bladder control, it is vulnerable to damage at various levels of the Central Nervous System, Peripheral and Autonomic Nervous Systems resulting in various types of Neurogenic Bladder.

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## Review Article

# COVID Management Strategy for Third Wave / Omicron Variant in India

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COVID-19, the worst Pandemic of this decade caused significant morbidity and mortality in the past 3 years and still continue to hit the human kind with its evil skills. After the first and second COVID-19 wave the third wave has emerged with new variants and with high transmission rate and reduced efficiency of treatments and vaccines. The main treatment strategy remain same as symptomatic and supportive treatments. Oxygen therapy, Steroid, Antivirals and some repurposed drugs like Ivermectin and newer drugs including monoclonal antibodies are used in this fight against COVID-19. Ivermectin is being the game changer in many states of India, they kept this medicine in their new treatment protocol also. Vaccination including additional Booster/Precautionary Dose along with the COVID appropriate behaviours, if we are able to maintain Physical distance, Wear mask properly, Wash our hands and Prevent crowd from gathering then we will not allow the virus to spread and prevent the emergence of another wave.

[J Indian Med Assoc 2022; 120(3): 56-61]

**Key words :** COVID-19, Omicron, Ivermectin, Booster dose.

COVID-19 is one of the worst viral pandemic in the last 100 years. The origin of the virus in Wuhan city of China in early December 2019 is a mystery and most likely the emergence was from a bat lineage via an unidentified intermediate host with more frequent human contact, in which the progenitor virus might have been circulating undetected for decades. The origin and spread of the disease created a havoc and feeling of unrest in India as well, affecting a population of more than 3.5 crore in India and more than 25 crore people globally. During this pandemic India lost more than 2000 doctors of modern system of medicine, they sacrificed their life for the fight against COVID-19<sup>1,2</sup>. We salute their sacrifice and pay tribute to their selfless services. Even though the spread of the disease in the country was very unfortunate the silver lining behind its spread was the COVID appropriate behaviour that the disease taught<sup>3,4</sup>. Awareness was created across the country over a very large scale like never before about the proper use of masks, cough etiquettes, physical distancing hand washing and sanitization. But never the late while we were almost recovering from the 2<sup>nd</sup> wave of covid, a new variant named OMICRON was detected in South Africa which became the major cause of 3<sup>rd</sup> wave in India.

### Current COVID-19 Epidemiology (Table 1) :

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### Editor's Comment :

- Third COVID-19 Wave with new variant including Omicron variant emerged as a threat for the society. However, India has contained this threat effectively because of its largest and fastest COVID-19 vaccination program including additional booster doses and COVID appropriate behavior.

### COVID-19 Variants and Emergence of Omicron :

Viruses like SARS-CoV-2 (COVID-19) continuously evolving and Genetic Mutations occur during replication of the Genome. A variant is a Viral Genome (Genetic Code) that contain one or more mutations. To assist with public discussion WHO proposed the name of this variants consisting of a Greek alphabet like Alpha, Beta, Gama etc. They are also classified them as Variant of Interest (VOI) and Variant of Concern (VOC) etc. VOI are the variant with Specific Genetic Markers associated with changes to receptor binding, reduced neutralizing antibodies by the Vaccine and reduced efficiency of treatments. VOC are those variant with high transmissibility, potential for severe disease, reduced effectiveness of treatments or Vaccines or diagnostic detection failure.

Some of the variants and the place of earliest documentation are given below :

Alpha (B.1.1.7)	– United Kingdom
Beta (B.1.351)	– South Africa
Gamma (P.1)	– Brazil
Delta (B.1.617.2)	– India
And finally Omicron (B.1.1.529)	– South Africa

The Omicron variant is a variant of SARS-CoV-2, the virus that causes COVID-19. It was first found in

COVID -19 Cases	Global	India	Uttar Pradesh
Total no of cases /Cases per million population	32.9 crores (329,009,077)/42,209	3.73 crores /26,683 (only 11.34% of total global morbidity)	18.3lakhs (only 4.9% of total national morbidity)
Mortality Total/per Million population	55.5 lakhs /713	4.86 lakhs/347 (only 8.75% of total global mortality)	22,963 (only 4.72% of total national mortality)/102
Case Fatality ratio	2.3	1.3	1.1

South Africa on 9<sup>th</sup> November, which was then reported to WHO on 24<sup>th</sup> November, 2021. On 26<sup>th</sup> November, 2021, the WHO designated it as a **variant of concern** and named it “Omicron”, the fifteenth letter in the Greek alphabet<sup>5,6</sup>. The variant has total of 60 mutations compared to the actual variant, significant number of mutations are affecting the spike protein, targeted by most COVID-19 vaccines at present. This level of variation has led to concerns regarding its transmissibility, Immune System Evasion and Vaccine Resistance. Omicron is believed to be far more contagious (spreading much more quickly), to multiply around 70 times faster than the Delta variant<sup>7,8</sup>. But to be less able to penetrate deep Lung Tissue. However, the extremely high rate of spread, combined with its ability to evade both double vaccination and the body’s Immune System, means the total number of patients requiring hospital care at any given time is still of great concern.

On 2<sup>nd</sup> January, 2022 Israel confirmed its first case of an individual infected with both the seasonal flu and COVID-19 at the same time named **FLURONA**, the two infections were found in an unvaccinated pregnant women who had mild symptoms. Another strain of covid-19 that combines delta and omicron was found in cyprus “**DELTACRON**”. WHO however has not given any official confirmation about the two strains and their nomenclature<sup>9,10</sup>.

Owing to the rapid spread of the disease due to its high infectivity Indian Council of Medical Research (ICMR) gave a guideline for COVID testing, to contain the spread of the disease in the Country.

**ICMR New Advisory for COVID Testing (10 th January) :**

Current COVID 19 testing strategy is for early detection of symptomatic cases for quick isolation and care and, early detection of infection in elderly >60 years and individuals with co-morbidities (Diabetes, Hypertension, Chronic Lung or Kidney Disease, Malignancy, Obesity etc for quick care. Test may be a point of care test like home or self test / Rapid Antigen test or Molecular Tests like RT-PCR, TrueNat, Cartridge Based Nucleic Acid Amplification Test

(CBNAAT), newer SARS-CoV-2 Omicron or Variant detection RT-PCR assays. According to the ICMR protocol, in community setting the following persons may get tested ; (1) symptomatic patients (Cough, Sore throat, Fever, Loss of taste/smell, Breathlessness and / or other respiratory symptoms), (2) at risk contacts of confirmed cases (Elderly >60 years and individuals with co-morbidities (Diabetes, Hypertension, Chronic Lung or Kidney disease, Malignancy, Obesity), (3) Individual undertaking International travel, (4) International travellers arriving at Indian Airport or Seaports. In hospital settings the testing may be undertaken as per the decision of the treating doctor. However patient care should not be compromised due to COVID testing so they included the following considerations like; emergency procedures, should not be delayed, should not be referred to other facilities for lack of a testing facility, asymptomatic patients undergoing surgical / nonsurgical invasive procedures including pregnant woman should not be tested unless symptoms develop<sup>11</sup> (Fig 1).

**TREATMENT**

Similar to 1<sup>st</sup> and 2<sup>nd</sup> wave strategy, the main treatment of the disease is symptomatic and supportive treatment . The mass casualties of COVID cases in previous waves were treated by Oxygen Therapy,

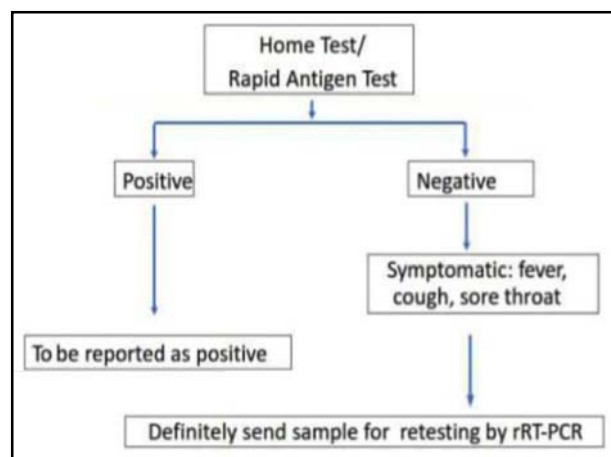


Fig 1 — Algorithm for COVID-19 Test Interpretation Using Home Test / Rapid Antigen Point of Care Test (Icmr, 10<sup>th</sup> Jan 2022)

Steroids and inhaled Budesonide and antivirals like, Remdesivir, Favipiravir. All of the drugs which are tried in the treatment of COVID-19 were repurposed drugs. The alternative treatment of COVID-19 consists of Ivermectin, Baricitinib (JAK inhibitor), Monoclonal Antibodies-Cocktail Therapy, Tocilizumab, Plasma therapy. The therapies recommended by AYUSH like Kadha, Steam, Yoga, Pranayama, Warm water etc were also widely accepted<sup>12-19</sup>.

Latest treatment protocol for the management of third wave of COVID-19 given below :

**AIIMS/ICMR COVID-19 Treatment Protocol (14/1/2022) :**

AIIMS/ICMR revised the COVID-19 treatment protocol on 14<sup>th</sup> January, 2022. They approved the off label use of Remdesivir and Tocilizumab in specific circumstances (Fig 2).

Ivermectin is a FDA-approved broad spectrum Anti-parasitic agent, Commercialized since 1981 but no resistance is detected till date. High efficiency and safety profile along with low cost of this medicine made this a preferred medication for common people. Ivermectin is considered as a wonder drug because of its different mechanisms of action. MOA which make this effective against COVID-19 are, inhibition of viral replication, Blockade of the entry of the virus into the

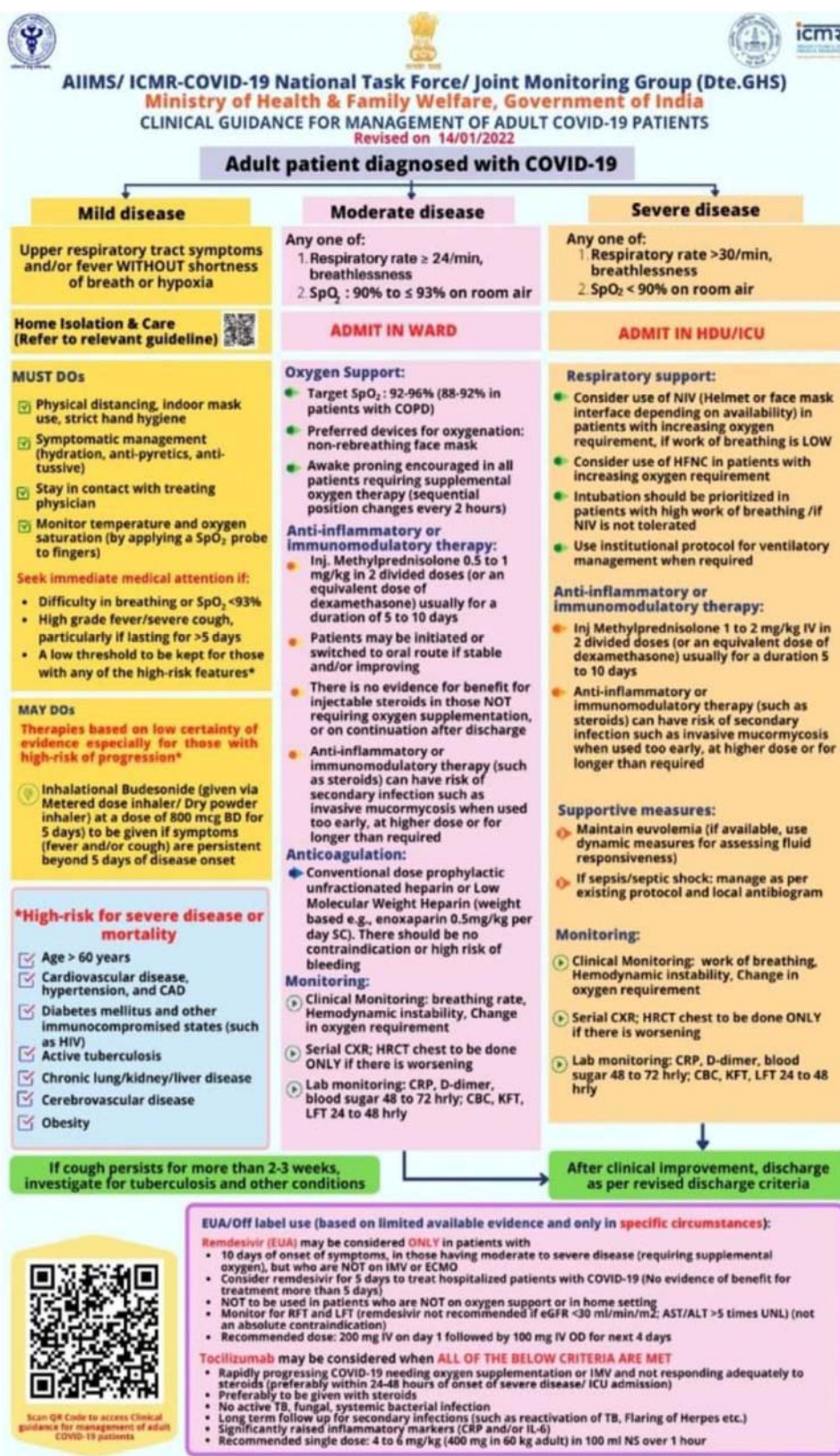


Fig 2 — Latest MOHFW/ICMR/AIIMS Guideline for Management of COVID-19 (Dated 14/1/2022)



### Ivermectin for COVID-19: real-time meta analysis of 75 studies

Covid Analysis, Jan 16, 2022, Version 172 — added Abbas [BBC, GMK response]

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- Statistically significant improvements are seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. All remain significant after exclusions. 49 studies from 45 independent teams in 21 different countries show statistically significant improvements in isolation (37 primary outcome, 34 most serious outcome).
- Meta analysis using the most serious outcome shows 66% [53-75%] and 83% [74-89%] improvement for early treatment and prophylaxis, with similar results after exclusion based sensitivity analysis (excluding all GMK/BBC team studies), for primary outcomes, for peer-reviewed studies, and for RCTs.
- Results are very robust — in worst case exclusion sensitivity analysis 60 of 75 studies must be excluded to avoid finding statistically significant efficacy.
- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 25% of ivermectin studies show zero events in the treatment arm.
- Multiple treatments are typically used in combination, which may be significantly more effective.
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants. All practical, effective, and safe means should be used, including treatments, as supported by Pfizer [Pfizer, TrialSiteNews]. Denying the efficacy of treatments increases mortality, morbidity, collateral damage, and endemic risk.

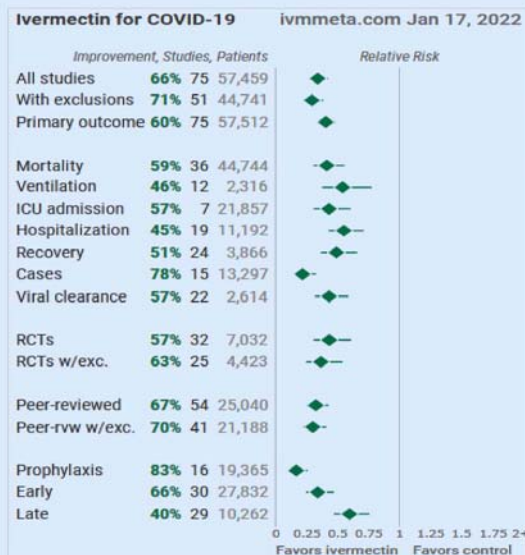


Fig 3 — Studies on the Effect of Ivermectin on COVID-19

Host Cell, Action as an Ionophore Molecule, Prevention of Microvascular Thrombosis and Sequestration in the pulmonary tissue. Currently there are 75 studies from 691 scientists in 24 Countries on the effect of Ivermectin for COVID-19 showed that there statistically significant improvement for viral clearance, hospitalization, mortality and recovery. They showed 59% lower mortality in 34 studies!<sup>20-25</sup> (Fig 3).

Earlier the Indian states Uttar Pradesh, Uttarakhand, Goa, Delhi, Kerala etc were officially approved the use of Ivermectin in COVID-19 treatment protocol. Uttar Pradesh was the first state which has officially approved the use of Ivermectin for COVID treatment.

Uttar Pradesh, one of the biggest and populated state of India but during COVID-19 pandemic this state showed excellent disease containment and effective management. It had only 4.7% of the total National COVID-19 mortality and case fatality ratio is also less than National ratio. Apart from the political and administrative commitment, intensive use of Health Experts in COVID-19 mangement and sensitization, and policies like Triple “T” policy (Tracing, Testing and Treatment) and Containment policy; health experts

says that the use of Ivermectin in the treatment of COVID-19 was also a reason for this excellent results. Till date very few states have published their treatment protocol for third wave of COVID-19 pandemic, Uttar Pradesh government have kept ivermectin in their treatment protocol due to the excellent results of this drug (Fig 4).

#### Revised Covid Protocol of UP (JAN 2022)

- Treatment of Mild Covid

ISOLATION.

IVERMECTIN 200 mcg/ Kg Body weight per day for 5 days.

Doxycycline 100 mg twice daily / Azithromycin 500 mg daily for 5 days .

PARACETAMOL SOS.

Vitamin B ,C,D .

- Prophylaxis of family Contacts of COVID-19 patient

Two Doses of 12 mg of IVERMECTIN , 1st Day and 7th Day.

- Prophylaxis of Healthcare Workers

IVERMECTIN 12 mg once a Week

Fig 4 — Revised COVID Protocol of UP (Jan, 2022)



There are various studies are conducting for some new drugs for COVID-19, and some of the accepted amongst them in this third wave of COVID-19 pandemic are given below (Advised by The COVID-19 Treatment Guidelines Panel<sup>26</sup>).

**Pre exposure prophylaxis :**

- Evusheld - Tixagevimab plus Cligavimab

**Therapies for mild to moderate High risk non hospitalized patients**

- Paxlovid Nirmatrelvir 300mg + Ritonavir 100mg BD for 5 days
- Sotrovimab 500 mg IV infusion
- Molnupiravir 800mg BD 5 days

**Postexposure prophylaxis for people:**

- Bamlanivimab and Eltesevimab 700mg + 1400mg
- Casirivimab and Imdevimab 600mg +600mg
- Sotrovimab 500mg (also active against Omicron)(Table 2).

**Preventive Strategy :**

Simple things that people can follow to prevent spread of COVID-19 like Namaste, Physical distancing, Take off Shoes, chappals before entering house, Hand wash, Wear mask when out of home, follow a healthy diet to boost immunity, Meditation, Yoga, Exercise, Good sleep. No addiction. Sanskar, respect and care of seniors, passionate environment at home. Work From Home. Tele consultation. Appropriate measures for Airborne Infection Control at Clinics and Hospitals. PPE kit, N95 masks during procedures.

Some actions are also required in the Country level also, WHO recommends acceleration of vaccination against COVID-19 and Booster/ Precautionary Doses for eligible groups, measures to increase the adherence of all individuals to protective measures, social measures to prevent crowding and people gathering in confined spaces , activating and prioritizing the case investigation and contact tracing for any COVID-19 cases, including Omicron; enhancing testing (and sequencing) and making it available freely to people with symptoms.

**COVID Vaccination :**

Vaccines which have mainly been available in India to fight against COVID, these are COVAXIN,

**COVISHIELD & SPUTNIK V.**

**Covaxin** was India’s first indigenous, whole-virion, inactivated vaccine developed by Bharat Biotech in collaboration with the Indian Medical Research Council (ICMR) and the National Institute of Virology (NIV). In July 2021, Bharat Biotech reported the vaccine to be 78% effective against symptomatic cases, 93% effective against severe COVID-19 infection and 65% effective against the Delta variant. **Covishield** on the other hand is the Indian modification of the Oxford–AstraZeneca COVID-19 vaccine in which instead of Chimpanzee Adeno virus Human Adeno virus is used. Currently these 3 vaccines are in use, however emergency use authorization has been given for 3 more vaccines which are Moderna, Johnson & Johnson, Zydus Cadila Zycova-D (3 doses, for 12 years and above)

First phase of vaccination was started on 16th January, 2021. Till now 157 crore doses have been given. UTTAR PRADESH VACCINATION (UPDATED on 17/1/2022)- Till now 22 crore doses have been given, Of which 8.59 crore are fully vaccinated. 13.7 crore have been given 1<sup>st</sup> dose .51,37,027 doses to children of age 15-18 and 3,87,596 precautionary doses were also given .

**Booster/ Precautionary Dose :**

Bharat Biotech said a study conducted at EMORY University demonstrated that subjects who received a booster dose of Covaxin six months after getting a primary two dose series have witnessed neutralising of the SARS-Cov 2 Omicron, Delta variants. Currently the booster dose of vaccination for Health Care Workers and high risk group has started in view of protection against the emerging new variants<sup>27</sup>. COVID-19 Vaccination of children in the age-group of 15-18 years to be started from 3rd January, 2022, vaccination option

Table 2 — Showing Comparison of Different Treatment Options in the Treatment of Nonsevere COVID-19 Disease

	Nirmatrelvir-ritonavir	Sotrovimab	Remdesivir	Molnupiravir
Efficacy (prevention of hospitalization or death)	Relative risk reduction: 88%	Relative risk reduction: 85%	Relative risk reduction: 87%	Relative risk reduction: 30%
Advantages	Highly efficacious Oral regimen Safe in pregnancy	Highly efficacious Safe in pregnancy Few/no drug interactions	Highly efficacious Studied in pregnancy Few/no drug interactions	Oral regimen Not anticipated to have drug interactions
Disadvantages	Drug-drug interactions	Requires IV infusion followed by 1-h observation	Requires IV infusion on 3 consecutive days	Low efficacy Concern: mutagenicity Not recommended in pregnancy/child

is "Covaxin" only. Health Care Workers (HCWs) & Front Line Workers (FLWs) or persons aged 60 years and above with comorbidities who have received two doses of COVID-19 vaccine after completion of 9 months another dose of COVID-19 vaccine provided from 10th January, 2022.

### Conclusion :

India as always has stood against the unprecedented challenges caused by the spread of COVID-19 infections, with both government and non-governmental cooperation. After the first and second COVID-19 wave the third wave has emerged with new variant with high transmission rate and reduced efficiency of treatments and vaccines. Vaccination including additional Booster / Precautionary Dose along with the COVID appropriate behaviours, if we are able to maintain physical distance, wear mask properly, wash our hands, and prevent crowd from gathering then we will not allow the virus to spread, rather this will also curtail the spread of infectious disease including Tuberculosis. The Public has now become wiser and aware on how to be healthy and have a check on their vitals via Pulse Oximeter for Oxygen saturation, Prone Position to maintain the Oxygen levels, Eating Healthy Diet to improve their Immunity. People now understand the importance of Social Distancing and other preventive measures prescribed by the Government with a good attitude. So together lets fight this war, this too shall pass.

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## Review Article

### Overview of END TB Programme

Supriya Sarkar<sup>1</sup>

With the success of RNTCP in achieving infrastructure and ecosystem, Government of India has started an ambitious plan to eliminate TB by adopting NTEP in 2020. It is a total government sponsored program involving all state and nonstate organizations. It involves early diagnosis with molecular methods; identification of drug resistant TB into INH mono-resistant TB, MDR-TB and XDR-TB; and management of TB with specific regimes. The program also adopted the National Strategic Plan based on 'Build-Detect-Treat-Prevent' strategy. The targets of NTEP are (i) to reduce estimated TB incidence rate to 44 (36- 158) per 100,000; (ii) to reduce estimated TB prevalence rate to 65 (56-93) per 100,000; (iii) to reduce estimated mortality due to TB to 3 (3-4) per 100,000; and (iv) to achieve zero catastrophic cost for affected families due to TB.

[J Indian Med Assoc 2022; 120(3): 62-5]

**Key words :** END TB, TB elimination, National strategic plan

**T**uberculosis (TB) was considered to be a curse, till the discovery of TB bacilli. Our fight against TB started with prayers and rituals, followed by sanatorium treatment with rest, good diet and fresh air. In 1956, Madras Chemotherapeutic Center had established that domiciliary treatment was not inferior to that of sanatorium treatment. The same institute in 1964 established the role of intermittent chemotherapy. National Tuberculosis Institute, Bangalore established the utility of 2 sputum smear examination over sputum culture of TB.

Several surveys were conducted in 1950s-60s and National Sample Survey, the most significant of them, was carried out between 1955-57 by Indian Council of Medical Research. The important findings were (i) prevalence of active TB cases varied from 13 to 25 per 1000 persons aged 5 years or above, (ii) the rate of bacteriological positive cases was 2-8/ 1000 population, (iii) prevalence in villages was not less than in cities, (iv) prevalence was lower for female than male, (v) prevalence in men showed continuous increase with age, (vi) prevalence was high in overcrowded slums, and (vii) majority of active cases had moderately advanced disease.

#### National TB Program- NTP (1962-1997) :

Based on the findings of surveys NTP was launched in 1962. The objectives of NTP were i) to identify and treat large number of TB patients so that infectious cases were reduced, and ii) to reduce the magnitude

#### Editor's Comment :

- Our aims to eliminate TB requires full hearted support of every quarter of health care providers.
- Private sectors should participate in the program by simple principle, ensuring patient to receive TB service while staying with private providers.
- Government is offering freemolecular tests and drugs, some of them are not available outside. We should not hesitate to utilize those facilities.
- Preventive treatment to house hold contacts and high-risk population is another important step. We can hope that with active involvement of all, we will definitely achieve our goal to eliminate TB.

of TB so that it ceased to be a public health problem. Organization of NTP included i) At central level - Tuberculosis Division in the Directorate General Health services; National Tuberculosis Institute, Bangalore and Tuberculosis Research Centre, Chennai; ii) At district level - District TB Committee, a functional unit of the NTP that supervised the District Tuberculosis Control Program; and iii) At peripheral level - Chest Clinics and Primary Health Centers (PHC).

Activities of NTP includes (i) Case detection, (ii) Case treatment, (iii) BCG vaccination, and iv) Health education. The program was revisited in 1992 and it was found that the situation did not change much. Despite a nationwide network of facilities, NTP failed to yield satisfactory results. Though the mortality rate decreased to 53/100,00 population, the case detection efficiency was only 30% and among them only 30% were treated successfully.

In prechemotherapy era, when no drugs were available, about 50-60% TB patients used to die, 20-30% patients were spontaneously cured and about 20% remained positive to propagate the disease to

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the community. Whereas, after implementation of NTP cure rate improved and death rate decreased but the 20% epidemiologically significant pool remained unchanged. Moreover, wild bacilli were being replaced by resistant bacilli. So, it appeared that to have an epidemiological impact we must reduce the 20% pool by increasing the cure rate above 85%. Case detection without achieving modest cure rate would be detrimental. Another important observation was that unsupervised use of rifampicin (R) may be dangerous as it would result in development of R-resistance (RR-TB). Moreover, a study conducted in Mumbai slum showed that more than 100 regimens were being prescribed for a single disease, tuberculosis. So, there was a need to standardized drug regimens.

#### **Revised National TB Control Program- RNTCP (1997-2020):**

Taking all those factors into consideration, Government of India launched RNTCP in 1997. The decision was encouraged by the results of Pilot studies done between 1993-94. The entire country was covered by RNTCP in March 2006 through unprecedented rapid expansion. The program is implemented by 100% sponsorship of central government. All components of Stop TB Strategy of WHO were implemented. RNTCP adopted the internationally recommended Directly Observed Treatment Short-course (DOTS), where all doses of anti-tuberculosis drugs (ATDs) are given under direct supervision. Sputum microscopy was adopted in a decentralized manner as a reliable diagnostic tool. Supply-channel of drugs was strengthened to assure regular supply of drugs. Sub-district supervisory units, TB Unit, were established to decentralize both diagnostic and treatment services.

Large-scale implementation of the RNTCP began in late 1998. In the first phase of RNTCP (1998–2005), the focus was on expansion of quality DOTS services to the entire country. RNTCP phase II from 2006 onward was designed to consolidate the gains achieved in RNTCP phase I, and to address TB/HIV, drug resistant TB (DR-TB) and to involve private sectors. Emphasis was given on training, operational research and involvement of non-governmental organizations.

The initial objectives were to maintain a cure rate of at least 85% in new sputum positive cases and to detect at least 70% of the estimated new sputum positive patients in the community. Other objectives added subsequently were to achieve 90% notification for all TB cases, to achieve 90% success rate of all new and 85% for re-treatment cases, to significantly improve the successful outcomes of treatment of DR-TB cases, to achieve decreased morbidity and

mortality of HIV/ TB cases, and to improve outcomes of TB care in the private sectors. On May 2012, a government order was issued to make compulsory notification of all TB cases. NIKSHAY, the web-based reporting for TB program, was initiated in 2012 that can transfer patients care informations from the remotest areas to monitoring institutions.

RNTCP was a felt-need program and over years several changes were adopted as per feed-backs from ground level and as per changes in WHO guidelines. Initially, regimens were given intermittently (thrice weekly) and that was been changed to daily regimen. Cat III regime was abolished. Similarly, no extension of intensive phase (IP) was allowed and ethambutol (E) was added in continuation phase (CP) along with isoniazid (H) and R. Ultimately, the regimen for drug sensitive TB (DS-TB) cases became 2 months of IP with H, R, E and pyrazinamide (Z); followed by 4 months of CP with HRE. Fixed drug combinations were introduced where each tablet contains R - 150mg, H – 75mg, Z - 400mg and E – 275mg for IP and R - 150mg, H – 75mg, and E – 275mg for CP. The number of tablets to be taken daily is decided by the weight of patients as per prescribed weight bands. Patients should be followed up during treatment by clinical assessment at least monthly; by sputum smear examinations at the end of IP and CP or when necessary and by chest x-ray (as on necessary basis). After completion of treatment, long term follow up should be done at 6, 12, 18 and 24 months. For certain extra-pulmonary TB like central nervous system, skeletal, disseminated TB etc., CP may be extended by 3 to 6 months based on clinical decision of the treating physicians and specialists of the particular field (for extension beyond 3 months).

Diagnostic facilities are provided by three tier system with i) at service / facility level—designated microscopy centres (DMC) for sputum microscopy and rapid molecular testing laboratories with facilities for Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and TrueNat for confirming TB and detecting Rifampicin resistant TB (RR-TB); (ii) intermittent reference laboratories (IRL) with facilities for 1<sup>st</sup> and 2<sup>nd</sup> line LPA (line probe assay), and culture and drug susceptibility testing; and (iii) National Reference Laboratories mainly to monitor quality control. TB cases are classified into 'Microbiologically confirmed TB' when TB bacilli are detected by smear, culture or molecular methods and 'Clinically diagnosed TB' when TB is diagnosed by clinical, radiological, biochemical or histopathological methods. Before starting treatment, TB cases are divided into DS-TB, H mono-



resistant TB, Multidrug Resistant (MDR)-TB and extensively drug resistant (XDR)-TB, and are treated by regimens specific for that classified TB category.

#### **World Health Organization (WHO) endeavor:**

WHO declared TB as global public health emergency in 1993, and that confiscates the long term neglect on TB. WHO also launched DOTS strategy for treating TB in 1997. WHO introduced 'The Global Plan to Stop TB 2011 – 2015' that will ultimately lead to elimination of TB. The 'END TB strategy after 2015', was approved in the sixty-seven World Health Assembly in May 2014.

The Vision of the strategy was to achieve a world free of TB, zero death, disease and suffering due to TB. The Goal was to end the global TB epidemic. The Milestones for 2025 were set as 75% reduction in TB death (compared to 2015), 50% reduction in TB incidence rate (less than 55 TB cases / 100000 population) and preventing affected families facing catastrophic economic cost due to TB. The Milestones for 2035 were set as 95% reduction in TB deaths (compared with 2015), 90% reduction in TB incidence rate (less than 10 TB cases / 100 000 population) and preventing affected families from facing catastrophic costs due to TB.

Principles of end TB strategy were (i) Government stewardship and accountability on monitoring and evaluation of the program; (ii) Strong coalition with civil society organizations and communities for implementation of the program (iii) Protection and promotion of human rights, ethics and equity; and iv) Adaptation of the strategy and targets at country level, with global collaboration. END TB strategy comprised of pillars including (i) Pillar I - early diagnosis, universal drug-susceptibility testing, TB/ HIV collaboration, preventive treatment, vaccination and screening of high-risk group; (ii) Pillar II - political commitment, resource mobilization, engagement of private sectors, case notification and infection control; (iii) Pillar III - discovery, development and approval of new tools, interventions and strategic plans; and research and innovation.

#### **National TB Elimination Program- NTEP (2020-till date):**

RNTCP has already achieved structural ecosystem like (i) mandatory notification of all TB cases, (ii) integration of the programme with the general health services (National Health Mission), (iii) expansion of diagnostic and treatment services, (iv) implementation of programmatic management of drug resistant TB (PMDT), (v) single window service for TB-HIV cases, (vi) national drug resistance surveillance and (vii)

revision of partnership guidelines. On the negative side, TB kills about an estimated 480,000 Indians every year and more than 1,400 every day. India also harbouring more than a million 'missing' (unnotified) cases every year. They are either undiagnosed or inadequately/unaccountably diagnosed and treated, mostly in the private sector.

Based on those background, RNTCP was renamed as National Treatment Elimination Program (NTEP) that has been made effective from 1 January 2020. NTEP is the public health initiative of the Government of India. It functions as a leading component of the National Health Mission and provides technical and managerial guidance to anti-tuberculosis activities in India. As per the National Strategic Plan (NSP) 2017-25, the program has a vision of achieving a "TB free India" and a commitment to achieve the END TB targets by 2025, 5 years earlier than global target.

NSP 2012-2017 had achieved universal accessibility to high quality diagnosis and management of TB. NSP 2017-2025 has been adopted in March 2017 by the Central Government with the aim to achieve 'TB Elimination'. The goal is to eliminate the curse of TB from India by adopting principals set by WHO. NSP for TB elimination 2017-25 is a framework to guide the activities of national and state governments, private sectors, civil society organizations, international agencies, research institutions, and other development partners. The program has a goal to achieve a "TB free India", under a strategic pillar of "Prevent (prevention of emergence of TB in susceptible populations), Detect (finding all DS-TB and DR-TB), Treat (initiating and sustaining free and appropriate anti-TB treatment to all cases) and Build (appropriate infrastructure and ecosystem)".

The Joint Monitoring Mission (JMM) gave exclusive recommendations to achieve END TB. They included surge of government funding for TB control (about 1500 crores/year), implementation of 'Standards for TB Care in India', incorporating private sector (ensuring patient to receive TB service while staying with private providers), enhancing the capacity of molecular diagnostic tests, managing DR-TB cases with newer drugs like bedaquiline, and sustained national campaign on "TB Free India/ TB Mukh Bharat".

The vision of the program is to achieve a TB-Free India with zero deaths, disease and poverty associated with TB. The goal is to achieve a rapid reduction of TB burden, mortality and morbidity while working towards elimination of TB in India by 2025. The objective of NTEP to be achieved by 2025 are:

- (i) To reduce estimated TB incidence rate to 44

(36- 158) per 100,000;

(ii) To reduce estimated TB prevalence rate to 65 (56-93) per 100,000;

(iii) To reduce estimated mortality due to TB to 3 (3-4) per 100,000; and

(iv) To achieve zero catastrophic cost for affected families due to TB.

To achieve those objectives, we must attain treatment success rate among DS-TB to 92% and that of DR-TB to at least 75%. Active case finding among the targeted population is another key instrument in TBEP. All TB patients must be notified before starting treatment. At least 90% of notified patients must receive financial support through direct benefit transfer. TB Preventive Therapy (TPT) should be started in at least 95% of eligible population (all house hold contacts and high-risk population).

NTEP is managed through four level hierarchy. At central level, there are Central TB Division (CTD) under the Ministry of Health and Family Welfare. A number of National Level Expert Committees and National Institutes work under CTD. The State TB Cells and District TB Office (~ 767) work at the state and district levels, respectively. About 6532 TB Units are working at sub-district level. About 20356 TB diagnostic centres (previously called DMC) are acting at peripheral level to diagnose and treat TB cases.

The challenges of NTEP have been augmented by the complex emergencies like the COVID-19 pandemic. In addition, the unfinished agenda of addressing the 'missing cases', scale up of TB care services in the private sector, providing social support to TB patients, TB preventive services, and addressing the social determinants of TB through a multisectoral approach continue to challenge the NTEP. They will remain the focus of NSP and NTEP over the next five years.

The requirements for moving towards ending TB/ TB elimination have been integrated into four strategic pillars 'Build-Detect-Treat-Prevent' that correspond with the four NSP objectives.

### Conclusion :

Question may be asked whether 'END TB' is possible. Most important positive point is that today human beings are the only reservoir of TB. Today, we have total political and administrative commitment towards achieving 'END TB'. On the other side, chronicity of the disease, long duration of treatment and emergence of three epidemics in India (much talked about epidemic of HIV, silent epidemic of diabetes and dangerous epidemic of DR-TB) have made our job difficult. Prevention of DR-TB is the most important factor as otherwise we will make a potentially curable disease incurable. That can be done by motivation and education of patients when they come to clinics. Patients must feel the warmth of health care givers and at the same time they must be warn about the consequences of irregular treatment. Regular home visit and 'defaulter retrieval' are key factors for prevention of DR-TB.

So, let us, the government sectors, private sectors, NGOs and social activists, come together to play our roles actively to achieve our target to END the curse of TB from India.

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## Case Report

# Cardiac Perforation by Permanent Pacemaker Lead, One Year after Implantation — An Unusual Occurrence and Its Management

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Delayed Cardiac Perforation by Permanent Pacemaker lead beyond one year of implantation is rare. It is also rarer in passive fixation lead, compared to active fixation lead. There is no Universal consensus regarding management of such cases with percutaneous *versus* surgical removal of the lead followed by re-implantation. Here we report a case of Right Ventricular (RV) perforation by a passive fixation permanent lead, in an 81-year-old lady, 14 months after implantation, who presented with Pacemaker capture failure but in hemodynamically stable condition. Pacemaker lead had migrated up to the Lower Lobe of Left Lung, Perforating Right Ventricle, pericardium and Left Pleura. We managed this case with open lead removal under direct vision by Lower Median Sternotomy, followed by implantation of an Epicardial Lead and Pacemaker.

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**Key words :** Permanent Pacemaker, Cardiac Perforation, Epicardial Pacemaker Implantation.

Device based therapies are becoming popular due to their excellent result and in most cases, non-availability of any alternate therapy. Complications due to such therapy are also becoming frequent. Iatrogenic Cardiac Perforation by Pacemaker or implantable Cardioverter Defibrillator leads is rare, accounting for 0.3% 0.8% of all pacing procedures<sup>1</sup>. Most of the cases occur within 24 hours of Device Implantation. But late onset (more than 1 month afterwards) Cardiac Perforations, which are even rarer, have also been described. Elderly, female sex and active fixation leads<sup>2</sup> are risk factors for such complications. Most studies have described it to be more frequent with active fixation (screwing) leads, where few others claimed it to be equal in frequency with passive fixation (tined) leads<sup>1</sup>. Due to its rarity, there is no Universal consensus regarding managing these patients with percutaneous-procedures *versus* Surgical removal of perforated leads followed by re-implantation. Here we report a case of Right Ventricular (RV) apical perforation and migration of a passive fixation Permanent Pacemaker lead into the Left Pleural Cavity, more than one year after successful implantation. Given the potentially life threatening complications due to Transvenous Lead removal, this patient was successfully treated with surgical off pump lead extraction, repair of the perforation followed by placement of Epicardial Pacemaker Lead.

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### Editor's Comment :

- Delayed perforation of Heart by Pacemaker lead is an extremely rare occurrence.
- Extraction of the culprit lead by open Surgery followed by implantation of Permanent Epicardial Pacemaker can be done safely and is a life saver.

### CASE REPORT

This patient, 81-year-old lady had undergone single chamber Permanent Pacemaker (Medtronic, VVI-R) implantation with passive fixation (tined) lead, placed percutaneously through Left Subclavian Venous Route, for symptomatic complete Atrio-ventricular Block. The Permanent Pacemaker lead was placed in Right Ventricular Floor. On Echocardiogram, she had structurally normal Heart with Normal Biventricular Systolic Function. Postoperative pacemaker parameters were satisfactory. She had routine follow up visit at 'Pacemaker Clinic' after one week, one month, three months and six months of implantation. All pacing parameters were satisfactory and patient was doing well.

After 14 months of implantation, the patient returned to the Emergency with Recurrent Syncopal Attacks. Electrocardiogram at Emergency Room showed Heart rate of 40 beats per minute with Pacemaker capture failure. She was immediately put on Temporary Pacemaker. Chest X-ray and subsequently Computed Tomography (CT) scan of Thorax had been done and Permanent pacemaker lead tip was found in Left Pleural Space touching the base of Left Lung, perforating through the RV Apex, Pericardium and Left Pleura.

Anticipating life threatening complications with transvenous lead removal, open surgical removal of the Pacemaker lead, was planned. After a Manubrium-sparing Lower Median Sternotomy, perforation site was identified and a pledgeted 4-0 Polypropylene Purse-string Sutures was taken around it. There were no collections in





Fig 1 — Initial Postoperative Chest X-Ray done after implantation of Permanent Pacemaker done 1 year ago.



Fig 2 — Chest X-Ray done 1 year later shows cardiac perforation by the permanent pacemaker lead (White arrow). The temporary pacemaker lead is also seen (Red arrow).



Fig 3 — Perforation of the cardiac apex caused by the permanent pacemaker lead (Yellow arrow) can be seen. The culprit lead then proceeds to perforate the pericardium and penetrate the left pleural space.

Pericardial and Pleural Sacs. The lead tip was carefully withdrawn from the Left Pleural Cavity, cut and removed. At the same time, the Permanent Pacemaker pocket was explored in the Left Subclavicular Region. Pulse generator along with the remaining lead had been pulled out and removed gently. RV Apical perforation site was closed by the previously taken purse-string suture. Subsequently another Epicardial permanent Pacemaker lead was implanted over the Right Ventricular Apex and its pulse generator was placed in a subcutaneous pocket created in the Epigastrium, approached through the same incision. After checking Haemostasis, an Intercostal Chest Drain was placed in the Left Pleural Cavity. The pericardium was closed using interrupted polyglactin sutures leaving multiple small pericardial windows. The Chest incision was closed in layers. Patient was extubated within a couple of hours after shifting to the Cardiac Surgery Postoperative Intensive Care Unit (ICU). The peri-operative period and follow up at 1 week, 15 day and 1 month were uneventful.

#### DISCUSSION

Late onset Cardiac Perforation by Permanent Pacemaker lead, beyond 1 year of implantation is a rare event. At times, it may be life threatening. High index of suspicion is needed to diagnose such cases, especially if the presentation is subacute. It should be considered in cases that present with atypical symptoms and a sudden change in electrical parameters during pacing interrogation<sup>3</sup>. CT scan of Thorax, along with Electrocardiography and Echocardiography, is an excellent modality of investigation, not only for diagnosing but also to assess the risk and damage to the surrounding Mediastinal Structures<sup>4</sup>. There is no clear-cut recommendation regarding management of such cases till date. Many studies suggested that transvenous lead extraction has good outcomes and open extraction

is rarely required<sup>5</sup>. But still there is a need to balance the risks of transvenous extraction against open extraction, as open extraction is relatively safer in term of repairing the perforation site under direct vision, identification and dealing with the damage to the surrounding Mediastinal Structures, if any.

#### CONCLUSION

Cardiac Perforation by permanent Pacemaker lead is extremely rare and delayed onset Cardiac Perforation by passive fixation lead is even rarer. CT Scan of Chest is an excellent modality for diagnosis. Extraction of the offending lead along with repair of the site of perforation and followed by implantation of a new permanent Epicardial Pacemaker can safely be done through Open Surgery.

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## Case Report

# Can a Neonate Shiver ? — A perioperative Diagnostic Dilemma and a Short Literature Review

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**Background:** Neonates often show involuntary movements peri-operatively which are difficult to diagnose. Neonatal Shivering albeit very rare, may confuse the anaesthesiologist by presenting as Seizures.

**Case :** A Neonate was scheduled for the repair of Lumbar Meningomyelocele in our Operating Room. At the end of an uneventful Surgery, we noticed jittery movements during recovery from Anaesthesia. Differentiating these movements from Neonatal Shivering, Motor Automatisms and Physiological New-born Behaviour was a challenge. The immediate venous blood gas analysis was within normal limits and no apparent cause could be found. Suspecting accidental Hypothermia, Immediate rewarming was initiated and after Consulting Paediatric Neurology intravenous Levetiracetam was given. There were no further similar episodes.

**Conclusion :** Shivering-like episodes in Neonates during the peri-operative period need to be carefully evaluated to allay parental anxiety, avoid inappropriate treatment and prevent any further complications.

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**Key words :** Neonatal convulsions, Benign, Shivering, Meningomyelocele, Hypothermia, MRI scan, Infant, Newborn, Diseases.

Neonatal involuntary movements have a unique presentation, quite distinct from the older age groups. The accurate diagnosis of these movements is challenging especially if they occur during the peri-operative period, since multiple possible etiologies such as a Neurological Pathology, the surgical procedure itself or even the anaesthetic technique used should be considered. A thorough pre-operative evaluation and meticulous management during the peri-operative period is imperative. We present the case of a Neonate presenting for excision of a Lumbar Meningomyelocele who had jitteriness during emergence from Anaesthesia.

Written informed consent was obtained from the parents to publish this case.

### CASE REPORT

A 13-day-old Neonate with a lumbar Meningomyelocele (MMC) was scheduled for Surgical Excision of the MMC. The 2.9 kg female infant was born at 38 weeks' Gestation by Cesarean Section (due to non-progress of labour) to a 32-year-old primigravida whose pregnancy was complicated by Intrahepatic Cholestasis of pregnancy. The neonate had Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores of 8 and 9

### Editor's Comment :

- Neonates may show abnormal movements in peri-operative period.
- The anaesthesiologist should be cautious to differentiate Shivering from Seizures or jitteriness and should intervene early to achieve better outcome.

at 1 and 5 minutes respectively and was alert, active and did not show any signs of neurological deficit. She was vaccinated with Bacillus Calmette Guerin (BCG), Oral Polio Vaccine and Hepatitis B Vaccine at birth and received an intramuscular Vitamin K injection. A Neurosurgery Consultation was done for the swelling over the lower back. On their advice a Magnetic Resonance Imaging (MRI) of the Spine was done which revealed a 5x4 cm Meningomyelocele at L5 Level with a Spina Bifida at L5-S1 Level and a low-lying Tethered Cord. The MRI brain was normal with no evidence of Tonsillar Herniation. The surgery was planned on day 13 of life. After an appropriate period of fasting, the baby was taken to the Operating Room (OR) and an intravenous induction was done using fentanyl, propofol and atracurium followed by securing the airway with a 2.5 mm Cuffed Endotracheal Tube with direct Laryngoscopy. After placing the neonate prone, Laminectomy of the L3-L4 spinous processes and excision of the MMC was performed. There was a small dural tear during the Surgery which was repaired. The intraoperative vitals were stable and there was minimal blood loss. Normothermia was maintained throughout the Surgery using a forced air warming device and warm fluids. The core temperature was monitored with a Nasopharyngeal Probe. We removed the probe a few minutes before extubating and the patient was exposed

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to the OR Temperature for a brief period. During recovery from Anaesthesia, the baby had Paroxysmal onset of jitteriness, clonic movement of the legs and the right upper limb with twitching of facial muscles (Supplementary digital content can be found in <https://jimatube.in>).

These movements could not be stopped by gentle physical restraint. We immediately covered the patient and started re-warming, following which the intensity and frequency of the movements diminished. The vitals were stable throughout this episode with no desaturation or Haemodynamic Disturbance. We took a trial of extubating after adequate recovery of muscle power and the Neonate maintained well on supplemental Oxygen by face mask. Oxygen saturation and respiratory efforts were maintained on room air trial as well. However, the Neonate did not cry and appeared sedated. These movements, albeit subtle by this time, continued shifting from one limb to the other at definite intervals. A venous blood gas analysis was done which showed a compensated Metabolic Acidosis (pH-7.36, pCO<sub>2</sub>-27 mmHg, pO<sub>2</sub>-41.9mmHg, HCO<sub>3</sub>-17.3 mmol L<sup>-1</sup>). Electrolytes, Blood Glucose and Lactate Levels were normal (Na<sup>+</sup>-136 mmol L<sup>-1</sup>, K<sup>+</sup>-5.1 mmol L<sup>-1</sup>, Glucose-104 mg dl<sup>-1</sup>, Lactate-1.3 mmol L<sup>-1</sup>). As we could not ascertain whether these movements were due to Shivering, Seizures or any Physiological new-born behaviour, a Paediatric Neurology opinion was sought. The neonate was examined in the OR itself and Intravenous Levetiracetam 100 mg was initiated on their advice. The Neonate was then shifted to the Neonatal Intensive Care Unit and Intravenous Levetiracetam was continued in the postoperative period. The postoperative course was uneventful, and no further episodes of abnormal movements were noted.

### DISCUSSION

Neonatal Seizures have a distinct presentation, Pathophysiology, and Electroencephalogram (EEG) findings when compared to older age groups due to the Immaturity of the Neonatal Brain<sup>1</sup>. As a result, they can be a challenge to diagnose especially if they occur in the OR. Seizures occur due to the imbalance between the excitatory and inhibitory Neuronal Discharges within the Cerebral Cortex and can be precipitated by various factors such as Metabolic Disturbances, Intracranial Bleed, Infections, Congenital Brain Malformations etc. They Manifest in the Neonates as Clonic, Tonic or Myoclonic Seizures which can be focal or generalized<sup>2</sup>.

Epileptic Seizures (movements that occur due to change in electrical activity in the brain) must be differentiated from normal Physiological New-born Behaviour that have a much better prognosis and often require no treatment. This is important so that appropriate treatment can be initiated where required and over-treatment avoided. These include Sucking movements,

benign Neonatal sleep myoclonus, Neonatal tremors, Jitteriness etc<sup>3</sup>. Motor automatisms such as bicycling movements of the lower extremities, repetitive mouth and tongue movements, tonic posturing can be differentiated from Seizures by their ability to be triggered with tactile stimulation and inhibited by restraint. These are Non-epileptic, but a Neurology workup may be necessary if they are associated with other clinical features to rule out any Neurological issues<sup>4</sup>.

Commonly used Anesthetic Agents can Precipitate Seizures especially during induction or emergence. Seizure-like phenomena with propofol have been widely reported while some other observations suggest that propofol may also have Anticonvulsant Properties<sup>5</sup>. Sevoflurane has also been shown to induce Epileptiform EEG and Seizure-like motor activity in children during anaesthetic induction and emergence<sup>6</sup>.

There has been a reported increase in incidence of seizures 7 to 10 days after vaccination with Mumps, Measles, Rubella (MMR) Vaccine<sup>7</sup>. Although there is no consensus about the delay of Surgery following vaccination, Ingelmo *et al* recommend that Elective Surgery be postponed for a week after inactive vaccination and 3 weeks after live vaccination as Anesthesia and Surgery may cause immuno-suppression and may also cause confusion between vaccination side-effects and postsurgical complications<sup>8</sup>. The Neonate in our case had been vaccinated with BCG, Oral Polio Vaccine and Hepatitis B Vaccine at birth. Whether these vaccines also increase the risk of Seizures needs further evaluation.

The primary Pathology in this case was a Lumbar Meningomyelocele and 17% of children with Meningomyelocele have associated Seizure Disorders. Most of these children have underlying Central Nervous System (CNS) Pathology to account for their Seizures such as Cerebral Cortical Dysplasia, Polymicrogyria and Cortical Dysgenesis<sup>9</sup>. However, the pre-operative MRI in our case did not show any evidence of brain pathology.

A few other differentials were also considered in our case. Collins *et al* reported 2 cases of jitteriness among New-borns where the only Biochemical Abnormality that could be found was Vitamin D deficiency. They suggested that Neonatal Tremors could be an early indicator of Vitamin D deficiency and should be considered in the work up of Neonates with no other known Pathology<sup>10</sup>.

Neonates predominantly maintain Normothermia using Non-shivering Thermogenesis although Brück *et al*. have noted that Shivering has been observed in Neonates with Severe Hypothermia after Birth<sup>11</sup>. Alexander *et al* suggested that shivering might occur if Non-shivering Thermogenesis had reached its full potential<sup>12</sup>. Propofol, fentanyl and inhalation agents have been shown to reduce Non-shivering Thermogenesis in Infants and could be an inciting factor in triggering Shivering in

Neonates<sup>13</sup>. Maintaining Normothermia is crucial in the perioperative period and this is especially true for Neonates who have underdeveloped Thermoregulatory Systems. On the other end of the Temperature Spectrum, Febrile Convulsions are a Common Cause of Seizure Disorder in Children with most of them occurring within 24 hours of fever onset<sup>14</sup>. The warming blanket used during anaesthesia can cause an increase in body temperature which itself can cause Seizures in a Neonate<sup>15</sup>. In our case, the small duration for which the Neonate was not covered with the warming blanket, could result in Hypothermia. Thus, Neonatal Shivering was considered as a differential diagnosis.

### CONCLUSION

Neonatal Seizures or seizure-like Phenomena during the perioperative period can be challenging to diagnose and manage, often leading to an increased duration of postoperative stay, increased parental anxiety and at times inappropriate treatment. One must consider all possible factors related to the patient, surgery and anaesthesia while searching for the etiology. Neonatal shivering, although rare, should be kept as a differential diagnosis of these abnormal movements.

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## Case Report

# Thrombocytopenia in COVID-19 : A Diagnostic and Therapeutic Challenge

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The World started to experience the wrath of pandemic in the form of SARS-COV 2/COVID-19 infection since 2020. It is not the first time that we are experiencing such life threatening pandemics. But, what we forget to remember is the known diseases that are always there around us along with this pandemic. COVID-19 has its affect on almost every Organ System and one of its complications being Thrombogenicity. In order to combat this condition, we are using Anticoagulant Therapy mostly in the form of unfractionated Heparin or Low Molecular Weight heparin. But, it is also evident that heparin itself can result in state of Thrombosis in the form of heparin-induced Thrombocytopenia Complex and thus worsening the condition of the patient if not identified and treated early. In this report, we are going to discuss about a case of Thrombocytopenia Associated with COVID-19 which might be provoked by COVID-19 itself or use of Heparin and have given a brief review of literature on this topic.

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**Key words :** COVID-19, Thrombocytopenia, Coagulopathy, Cytokine storm.

The most common presentation of Thrombocytopenia is Petechiae<sup>1</sup>. Some of the causes of thrombocytopenia are drug induced (Cytotoxic Drugs), Bone Marrow Failure / Infective Hematopoiesis (Aplastic Anemia and Leukemia), Inherited (Wiskott-Aldrich Syndrome), immune-mediated destruction (Heparin Induced Thrombocytopenia and Idiopathic Thrombocytopenic Purpura) Non-immune Mediated Destruction (disseminated intravascular coagulation) and Hypersplenism<sup>2</sup>.

In other hand, we are presently encountering the COVID-19 pandemic which itself has a wide variety of presentation even though its major complications are in the Respiratory System<sup>3</sup>. It has been evident that COVID-19 infection has multi-organ involvement due to a number of mechanisms such as Coagulopathy, thrombocytopenia and Cytokine storm<sup>4-6</sup>. In our case report, we are trying to relate a case of COVID-19 and Thrombocytopenia and find out a possible co- relation if any.

### CASE REPORT

A 64-year-old known hypertensive male was admitted with complain of dry cough and fever for last

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### Editor's Comment :

- Thrombocytopenia per se, is not an usual hematological manifestation of COVID-19.
- Low platelets count in a patient with COVID-19 should make the physician aware of several other etiologies, such as co-infections (Dengue, Malaria or Scrub Typhus), drugs (heparin, low molecular weight heparin, antibiotics) and sepsis associated with disseminated intravascular coagulation.

two days. On presentation, his peripheral Oxygen Saturation (SpO<sub>2</sub>) was 79% on room air, respiratory rate of 24/min, blood pressure of 140/90 mm Hg; his Chest on auscultation had bilateral mild and basal crackles and otherwise physical examination was unremarkable. He was Non-diabetic and was on regular Anti-hypertensive medication since his diagnosis 2 years back. His past history and family history was unremarkable. Reverse Transcription–Polymerase Chain Reaction (RT-PCR) from nasopharyngeal and oropharyngeal swab for COVID-19 came positive. He was started with supplemental Oxygen and other supportive therapy as per the standard guideline of COVID-19 management. He was started on Anticoagulants (Enoxaparin at the dose of 60 mg twice a day by subcutaneous route) due to presence of Pneumonia in Chest Radiography and elevated D-dimer levels. He was changed to unfractionated Heparin as he started to show signs of Acute Kidney Injury from day 4 of his hospitalisation. In the following days, his condition was improving, his Oxygen demand was decreasing and Renal Functions also started improving. On day-8 of his hospitalisation, he started developing



dyspnea as his SpO<sub>2</sub> started to decrease ranging from 76%-85% and was then maintained in Non-invasive positive pressure support. His blood counts showed Platelet Count around 40000/uL whereas Total Leukocyte count was 8500/cumm, Hemoglobin was 10.0gm/dl. His blood reports on the next few consecutive days were unremarkable except the Platelet Count range from 40000/uL to 50000/uL; he was having no signs of bleeding or petechial rashes. He suddenly had Cardiac arrest and was unable to resuscitate.

### DISCUSSION

The COVID-19 pandemic has successfully created a huge impact on the lives of every human being. We as Healthcare professionals forms a distinguished part of the Healthcare System getting an ample of opportunity to observe, discuss and develop new ways to combat this Viral Infection. COVID-19 infection affects the Respiratory System mainly but it also has a role in our Vasculature and may cause Vasculitis, Thrombosis, Thrombocytopenia and as a result affecting the other Organ Systems as a whole<sup>7</sup>. We are advised to administer anticoagulants mostly unfractionated Heparin or Low Molecular Weight Heparin to combat the coagulopathy seen with COVID-19 infection<sup>8</sup>. In our case scenario, the patient was admitted with COVID-19 infection was having normal levels of Platelet Count till day 7 of his hospitalisation. In the above case study, the most common causes of fever associating with thrombocytopenia like Dengue, Malaria, HIV, septicemia, Tuberculosis were ruled out and the patient had only two days history of fever throughout the entire period. Our patient's condition deteriorated suddenly after day-7 of his hospitalisation developing Dyspnea and Thrombocytopenia. In this scenario, where the patient was infected with COVID-19 infection; increasing Dyspnea draws our attention to mostly worsening of COVID-19 infection and thus we acted accordingly. But unfortunately, we were not alerted by the warning signs of Thrombocytopenia associating with administration of Heparin. The patient's Platelet Count decreased below normal level and varied from 40000-70000/uL though he showed no signs of petechial rashes. The increasing Dyspnea can be due to an event of Micro-Thromboembolism affecting pulmonary circulation which was not ruled out due to Lack of proper radiological intervention, thus leading to sudden Cardiac arrest. Platelet Factor-4 (PF-4) has one of its functions in promoting blood coagulation in response to infection. In Respiratory Virus Infection PF4 stimulates antigen presenting cells, thus

stimulating natural killer-cells and Lymphocytes. PF4 also shows great affinity to bind with Heparin due to surface charge differences. This heparin-PF4, PF4Ab together constitutes the Heparin Induced Thrombocytopenia (HIT) complex thus facilitating the production of Procoagulant Cytokines<sup>9</sup>. On the other side, COVID-19 infection also facilitates Coagulopathy even though there is less common chances of Prothrombin Time (PT) or Activated Partial Thromboplastin Clotting Time (aPTT) prolongation or evident Thrombocytopenia or bleeding manifestations<sup>10</sup>. The immune mediated response due to Cytokines, Hypoxia, Endothelial damages leads to thrombosis in COVID-19 infection<sup>11</sup>. These Thromboses are capable to cause both arterial and Venous Thromboembolic events and it is also evident from various studies that these Thrombotic events can affect the Pulmonary Vasculature too. But, in COVID-19 infection there is both increased Platelet Consumption and increased Platelet production thus leading to mild or no Thrombocytopenia<sup>12</sup>. In our case scenario, the Patient started to deteriorate in his condition suddenly from day-8 of his hospitalisation even after improving in his clinical condition; this gives our suspicion more towards HIT rather than only COVID-19 infection even though we failed to diagnose it on time. Thus, this Thromboembolic event may have led to the Cardiac Arrest of the patient.

### CONCLUSION

In order to prevent Thrombogenicity in COVID-19 infection, we are mostly using Heparin. In many cases it has helped to limit the mortality but in some cases we still lose our patients. Sometimes, conditions such as HIT leads to further worsening the case scenarios by inducing coagulopathy. Hence, further detailed studies are required to prevent such preventable events of Coagulopathy while managing moderate to severe cases of COVID-19 infection.

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## Voice of Expert

### Medical Certificate of the Cause of Death : Some Tips for the Clinician

Somnath Das<sup>1</sup>

#### **(Q.1) What are the basic rules in India for writing a death certificate?**

**Ans :** At the very onset let me make it clear that the terminology “Death certificate” is not identical with “Medical Certification of Cause of Death (MCCD)”.

Medical certification of cause of death is issued by the registered medical practitioner, whereas the Death Certificate is issued by the Municipal corporation authority or by the Gram Panchayat as the case may be.

The documents - “Medical certification of cause of death” and the Death Certificate”, both are governed by the Registration of Birth and Death Act 1969 and are following the WHO formats accepted and published by the office of the Registrar General, Government of India in September 2012.

The basic principle of writing MCCD is as follows -

(A) MCCD can be issued by any registered medical practitioner who had attended the patient during his last illness. When confronted with the death of a person, a registered medical practitioner has to do two jobs, first, he should diagnose and declare death and then issue the medical certification of cause of death.

(B) MCCD can be issued only in cases of natural death where the doctor is satisfied with the cause.

(C) Should be written as per the WHO format form number 4 (for institutional deaths) or 4A (for the private practitioners or Non-institutional deaths).

(D) The MCCD should be issued free of charge as per the registration of Birth and Death Act 1969 section 10 (3).

#### **(Q.2) If a person had died at home without any medical supervision, who will write the death certificate?**

**Ans :** A Registered medical practitioner can not issue an MCCD in such cases. As per rule, no certificate is issued in cases of expected, explained, and died under suspicious circumstances. These deaths are to be registered as Brought Dead” cases

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in the nearest Health care facility and will be subjected to postmortem examination to determine the cause of death.

#### **(Q.3) If no doctor had seen a person for a long time before death, who will write the death certificate?**

**Ans :** If you look at the regulations on Medical certification of cause of death prevailing throughout the world, there are essentially two schools of thought. As per the Textbook written by Simpson on Legal Medicine, those doctors who have attended the patient during his terminal illness or within 14 days before his death can issue the certificate. Again as per the recommendation by the Broderic Committee, a doctor who has attended the patient at least once during the seven days preceding death can issue a certificate. If we consider the above two documents the maximum time limit permitted for giving the certificate can be accepted as 14 days before the death of the patient. Naturally, a doctor who had seen the patient a long time before death but has not attended during his/her terminal illness within 14 days of the event, cannot issue any certificate. All such deaths attended by a medical practitioner at to be reported as medico-legal deaths and will be subjected for post mortem examination.



(Prof) Dr Somnath Das

**IN INDIA, A LOT OF ORDINARY PEOPLE DIE AT HOME FROM NATURAL CAUSES. MOST OF THEM HAD NOT VISITED ANY DOCTOR FOR A LONG TIME. IS IT REALLY POSSIBLE TO DO POST-MORTEM IN ALL THESE CASES?**

**IN UK OR USA, A PERSON NEEDS TO BE REGISTERED WITH A GP AT ALL TIMES. THUS, HE/SHE IS ALWAYS UNDER MEDICAL SUPERVISION. IN INDIA, PEOPLE DO NOT HAVE SUCH PROLONGED CONTACT WITH DOCTORS. THUS, THE RULE OF STAMPING UNATTENDED DEATHS AS “MEDICOLEGAL” PROBABLY NEEDS TO BE CHANGED. THE**

**CULTURE OF THE INDIAN SOCIETY IS TO GO TO A DOCTOR ONLY WHEN A PERSON STOPS BREATHING. THAT PERSON MAY HAVE NOT BEEN IN CONTACT WITH THE MEDICAL SYSTEM FOR DECADES. IF WE START RECOMMENDING POST-MORTEM FOR ALL THESE CASES, THE SYSTEM WILL BE OVERWHELMED AND IT WILL BE A TRAUMA FOR THE FAMILY TOO!**

**(Q.4) What are the essential facts to be mentioned in a death certificate?**

**Ans :** Both forms number 4 and 4A consists of two segments - the part above the dotted line which is to be retained and the part below the dotted LINE which is to be handed over to the patient party.

The upper part consists of two sections, of which the first contains the epidemiological information about the deceased; whereas the second section is the Cause of Death part containing the immediate cause, the antecedent cause, and the underlying cause (PART 1). Other significant conditions contributing to the death may be included in (PART 2).

If confident, the Registered medical practitioner may fill up the manner of death section.

This is to be remembered that the bottom portion of the medical certificate of cause of death is to be filled up also by the certifier. It has to be detached and handed over to the relatives. This document enables them to get the Municipal permission for cremation as well as it acts as a reference to obtain the extract of the death register which is known as the 'Death Certificate' from the registering authority.

**(Q.5) Should the death certificate be issued only in Form 4A? can it be written in the doctor's letterhead?**

**Ans :** Form number 4 is for institutional deaths and form number 4A is for the non-institutional deaths/private practitioners. It is always preferable to issue the Medical certificate of cause of death in form number 4A for the private medical practitioners. It can be written on doctor's letterhead but it must contain all the segments written in form 4A.

**(Q.6) If a person dies of old age without any significant disease, what should be written as the cause of death?**

**Ans :** Death due to old age is also a natural death and the underlying cause of death can be entered as 'senility' under 1(a) row. However, it is to be

remembered that senility as the underlying cause of death can only be entered when the doctor is satisfied that no other disease or complication has caused the death.

**(Q.7) Can a doctor write death certificate of a close family member like his own mother or brother?**

**Ans :** Though there is no such hard and fast rule mentioned in the Registration of birth and death Act is, it is preferable not to issue death certificates of closed relatives as there is a possibility of conflict of interest.

**(Q.8) If a person dies while being transferred from one hospital to another, who writes the death certificate?**

**Ans :** In such cases the transferring hospital in which the patient was first attended in living condition, should issue the death certificate if the attending physician is confirmed with the cause of death.

**(Q.9) If a person dies from a notifiable disease like cholera or dengue at home, should the doctor inform any health authority? if yes, then whom? and through what means (in writing, by sms, by e-mail, verbally over phone)?**

**Ans :** Notifiable disease is any disease that is required by law to be reported to the government authorities. Any registered medical practitioner needs to notify search diseases in proper format (if unavailable, on their letterhead) within 3 days or verbally via phone within 24 hours depending on the urgency of the situation.

They will give such notification to local health authorities like BMOH or CMOH or Municipality Health Officer as the case may be.

**WHAT ARE THE PROBLEMS THE DOCTOR MAY FACE IN SUCH CASES? CAN A DOCTOR FACE GOVERNMENT ENQUIRY AND HARRASSMENT IN SUCH CASES?**

**(Q.10) If a doctor is requested by his colleague to write the death certificate of a patient, should the doctor do so based on the information received from his colleague?**

**Ans :** Medical certification of cause of death is to be filled up by the doctor who has full knowledge of the patient. Even in partnership practice, one doctor should not certify the cause of death to his colleague's patient unless attended the deceased in the past.



**(Q.11) Can “cardiorespiratory failure” be written as a cause of death?**

**Ans :** Terminal events, like a circulatory failure, respiratory failure, etc. are modes of dying and should be avoided as they are no more than signs of death and provide no useful information as to the underlying disease process.

If at all it is to be written, the underlying disease which is related to such condition must be entered in the next line. They cannot be the sole entries.

**(Q.12) If a person is killed by means of an untraceable poison, the doctor may not be able to detect any foul play. In that case, if a doctor issues a death certificate in good faith, can he be charged with felony later?**

**Ans :** It is to be emphasized that no certificate is to be issued in case of sudden death where the death is unexpected or unexplained and under suspicious circumstances. The doctor can be charged under section 34 or Sec 212 of IPC. The doctor may be charged for concealing a crime to screen the accused person from legal punishment.

**(Q.13) If a doctor goes to a house to issue death certificate and suspects foul play, how should he inform the authority? which authority should be informed and how? should a doctor go to the police station by himself to report foul play? if so, which police station? the station nearest to the deceased person’s home or the one nearest to the doctor’s place of work?**

**Ans :** In such a situation the doctor may fill up the first part of the form 4A, but not the bottom portion of the Medical certificate of cause of death. Under the column of “cause of death” in form 4 or 4A, the doctor should write “The cause of to be determined by post mortem examination”. The registered medical practitioner must inform the nearest police station about the incident in writing or through any other electronic means which can be preserved for future correspondence.

Under Kolkata Police jurisdiction such complaints can be lodged through the online portal.

**WHAT ARE THE LEGAL IMPLICATIONS FOR A DOCTOR IN THOSE CASES? JUST TO LODGE A COMPLAINT, THE DOCTOR WILL HAVE TO SPEND A LOT OF TIME. THEN, THERE WILL BE UNENDING POLICE PROCEDURALS AND LEGAL BATTLES. CAN A DOCTOR REALLY AFFORD TO ENTER THIS UNENDING LEGAL QUAGMIRE?**

**(Q.14) In the age of telemedicine, can a doctor issue death certificate via telemedicine?**

**Ans :** It is not legalized to issue death certificates via telemedicine.

**IF THE PATIENT WAS LAST SEEN BY A DOCTOR (IN A DIFFERENT CITY) VIA TELEMEDICINE BEFORE DEATH, THEN WHO ISSUES A DEATH CERTIFICATE? SINCE DEATH CERTIFICATE MUST BE ISSUED FREE OF CHARGE, WHO WILL BEAR THE EXPENSES FOR THAT DOCTOR TO TRAVEL TO A DIFFERENT CITY, IF AT ALL POSSIBLE?**

**(Q.15) What are the common mistakes committed by doctors while issuing death certificate?**

**Ans :** As per the media reports and studies which have revealed that proximately 50 to 60% of medical certificates of cause of death submitted to the death registering authority are incorrectly filled up. The common mistakes are

(a) In section I of the Cause of death column of Form 4 and 4A there is a practice of writing different modes of death (cardio-respiratory failure) in place of cause of death.

(b) Not writing the events in proper sequence.

(c) Writing multiple underline causes in part 1 of the form.

(d) Major contributing causes are omitted

(e) Underlying cause listed as a contributory cause in part 2.

(f) Not writing the ICD classification of the disease.

(g) Manner of death should preferably be written when the registered medical practitioner is confirmed about it.

(h) Registered medical practitioner has no right to withhold the issuance of a medical certificate of cause of death even if his dues have not been cleared.

(i) No medical officer should sign the medical certificate in advance without examining the dead body personally.

(j) Issuing death certificates in sudden death cases.

(k) Not mentioning the registration number of the doctor.

(l) Using abbreviations in writing the cause of death.

**Dr Somnath Das thank you for the valuable insight into ‘Cause of Death’.**

## Pictorial CME

### PET-CT Scan Appearance in Aortoarteritis

Rudrajit Paul<sup>1</sup>

**H**eadache is one of the commonest symptoms in medical practice<sup>1</sup>. In different studies, it has been seen that headache can account for up to 10% of all GP visits and up to 33% of all neurology referrals<sup>1</sup>. While the majority of headaches comprise of primary causes like Migraine, there are some secondary causes which need elimination. We here describe one such secondary headache with the diagnostic imaging details.

#### The Report :

An 80-year-old woman complained of recurrent severe holo-cranial headache for two months. She was a known hypertensive, on two anti-hypertensive drugs. There was no past or recent history of head trauma, fever or vertigo. The headache was self-described by the patient as “nagging most of the times with intermittent bursts of severe pain”. The pain was often present at night and it disturbed sleep. At presentation this time, the pain was described as 7/10 in VAS (VisualAnalog Scale).

There was no local temporal tenderness. All cranial nerve functions, including vision were normal. There was also no focal neurodeficit or pyramidal signs. All peripheral pulses were palpable and symmetrical.

A contrast enhanced CT scan of the brain was normal, ruling out any SOL or infective focus. Finally, in view of the persistent headache, a PET-CT scan of the great vessels was done. This revealed (Fig 1) that the ascending aorta, aortic arch, descending aorta, subclavian and axillary artery walls were thickened (maximum wall thickness of descending thoracic aorta being 6 mm) with increased FDG uptake (SUV<sub>max</sub>: 4). Walls of bilateral common carotid arteries were also thickened with SUV<sub>max</sub> 3.6. Walls of abdominal aorta, renal arteries and bilateral common iliac arteries were also thickened (Max. wall thickness of abdominal aorta: 4 mm), with SUV<sub>max</sub> of 3.8. The PET-CT features were suggestive of aortoarteritis. There was no luminal narrowing. There was mild para-aortic fat stranding and a few inflammatory lymph nodes in the

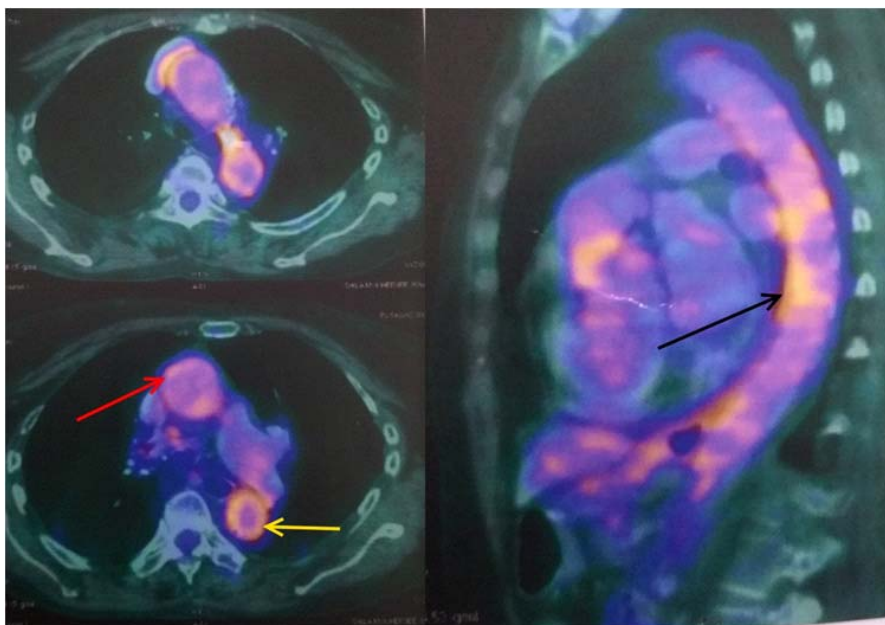


Fig 1 — PET-CT appearance of Aortoarteritis in the patient showing wall thickening with increased FDG uptake in ascending aorta (Red arrow), descending aorta (Yellow arrow) and thoracic aorta (Black arrow)

mediastinum.

Large vessel vasculitis has no definite serological test for diagnosis. The diagnosis rests on the tripod of clinical suspicion, assessment of response to steroids and recently, some imaging studies. *Of the imaging studies, the most useful is PET-CT scan.* FDG PET scan can detect not only the site of vascular inflammation, but also the degree of inflammation<sup>2</sup>. Thus, this is not only useful for detection of the condition, but also for follow up and early diagnosis of recurrence<sup>2</sup>. The exact cut-off for SUV max to detect active aortoarteritis varies with the researcher, but the generally accepted cut-off level is approximately 2.1<sup>2,3</sup>. By comparison, the SUV max of vessel walls in our patient was above 3.5 at all sites.

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<sup>1</sup>Consultant Physician, Kolkata

## Image in Medicine

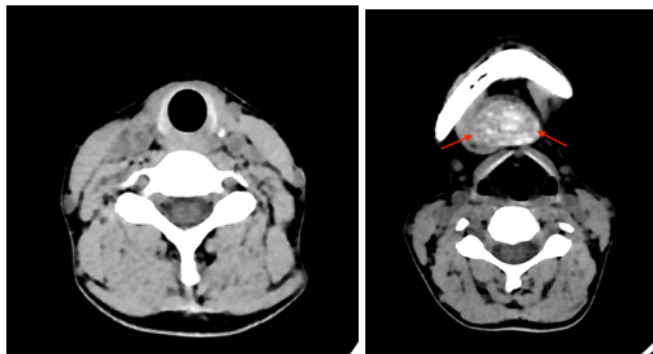
**Bhoomi Angirish<sup>1</sup>, Bhavin Jankharia<sup>2</sup>**

### Quiz 1

**A 23-year-old female presented with weight gain and lethargy.**

**Questions :**

- (1) What is the diagnosis ?
- (2) What are the locations of ectopic thyroid gland?



### Answers :

(1) Thyroid gland is not seen at its normal location, which is anterior to laryngeal cartilages. Hyperdense tissue (red arrows) is seen in sublingual location representing ectopic thyroid gland.

(2) During embryological development, the thyroid gland migrates down from the foramen cecum at posterior aspect of tongue to its location in the infrahyoid neck. This normal migration can be halted at any point resulting in ectopic thyroid gland. The ectopic locations of thyroid gland are : lingual (at base of tongue), sublingual (below the tongue), and other sites like mediastinum.

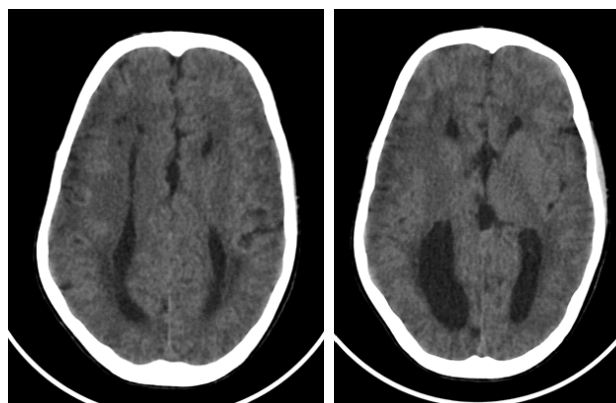


### Quiz 2

**A 11-year-old boy presented with cognitive deficits and seizures.**

**Questions :**

- (1) What is the diagnosis?
- (2) What are the associated conditions?



### Answers :

(1) There is disproportionate prominence of occipital horns of the lateral ventricles suggestive of colpocephaly. The ratio of the posterior horn to anterior horn of lateral ventricle width is  $\geq 3$ .

(2) Colpocephaly is associated with dysgenesis or agenesis of corpus callosum (as seen in midsagittal image, there is agenesis of corpus callosum). Pericallosal lipoma can also be associated with this condition.



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## Student's Corner

### Become a Sherlock Holmes in ECG

M Chenniappan<sup>1</sup>

#### Series 3 :

#### “Linked Lie”

This the stress ECG of 68 year-old-man who c/o palpitations during 1<sup>st</sup> stage and exercise was stopped. This ECG is 1 minute into recovery.

#### Questions :

What will you not do except :

- (1) IV adenosine
- (2) Early CAG
- (3) Start b blockers, antiplatelets and statins
- (4) Ask a question

#### Answers 4 :

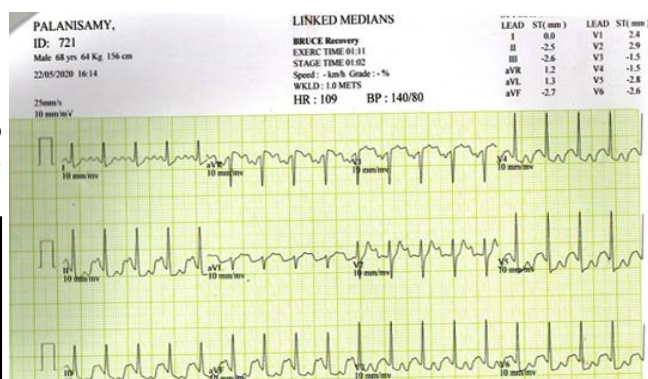
Ask the Question — Where is the Raw Data ?

#### ECG FINDINGS :

The post stress recovery ECG shows sinus tachycardia with infero lateral horizontal ST depression. There is ST elevation in avR. There are regular p waves in ST segment which are non-conducted. The overall interpretation of this ECG is likely to be significantly positive stress test, likely to be Triple Vessel Disease with Left Main Coronary Artery critical occlusion. In addition, there seems to be paroxysmal Atrial Tachycardia with 2:1 ventricular response.

But, please look at the top of the ECG which says “Linked Medians” which indicates that leads L I to V6 ( all 12 leads) are generated by the computer from the real raw ECG data of the patient. This type of linked medians is generated by the computer to give clean ECG complexes without muscle or somatic tremor artefacts as well as baseline wanderings which usually happen in real raw ECG data from the patient, who is exercising. It is important to realize that these linked medians which are generated by the computer are reliable only when the patient’s real raw ecg data of the exercising patient is good and regular. If the patient’s raw ECG data is corrupted due to muscle artefact or baseline wanderings due to inadequate preparation of skin and poor contact of electrodes with the skin, the linked medians are not reliable, as the computer tends to generate abnormal ECG complexes from the corrupted real raw data. This is what happened in this ECG. The real raw data of ECG is seen in L II rhythm strip at the bottom (Fig 1) which shows sinus tachycardia with fast upsloping ST depression and frequent Ventricular Ectopics (VPDs). If you compare this L II with linked medians of L II above, both look completely different. The presence of frequent VPDs had confused the computer and computer is generating a falsely

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abnormal ECG with ST depression and paroxysmal atrial tachycardia. But really patient had none of these changes according to raw data. The palpitation was due to VPDs rather than due to “Pseudo Atrial Tachycardia”

#### CLUE :

As the linked medians in this ECG, are misleading as strongly positive stress test with Atrial Tachycardia, the linked medians are lying because of the raw data in L II rhythm strip at the bottom shows only fast upsloping ST depression and Ventricular Ectopics. Because of this the clue of “Linked Lie” is given.

#### PRACTICAL IMPLICATIONS :

If one believes the linked median in this ECG, the patient will be treated wrongly with anti-arrhythmic drugs as well as will be subjected to unnecessary intervention such as early Coronary Angiogram (CAG). This will result in excessive anxiety, dangers of anti-arrhythmic drugs as well as excessive expenditure of CAG. As far as real raw data, the patient does not require any of above drugs or investigations. So the lesson in reading the stress ECG recordings is that one should only look at raw data and not the computer synthesised linked medians. To get the clear raw data without artefacts, good skin preparation and proper application of electrodes are needed.

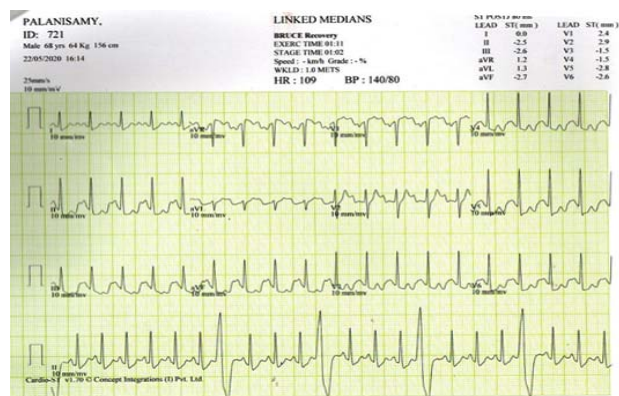
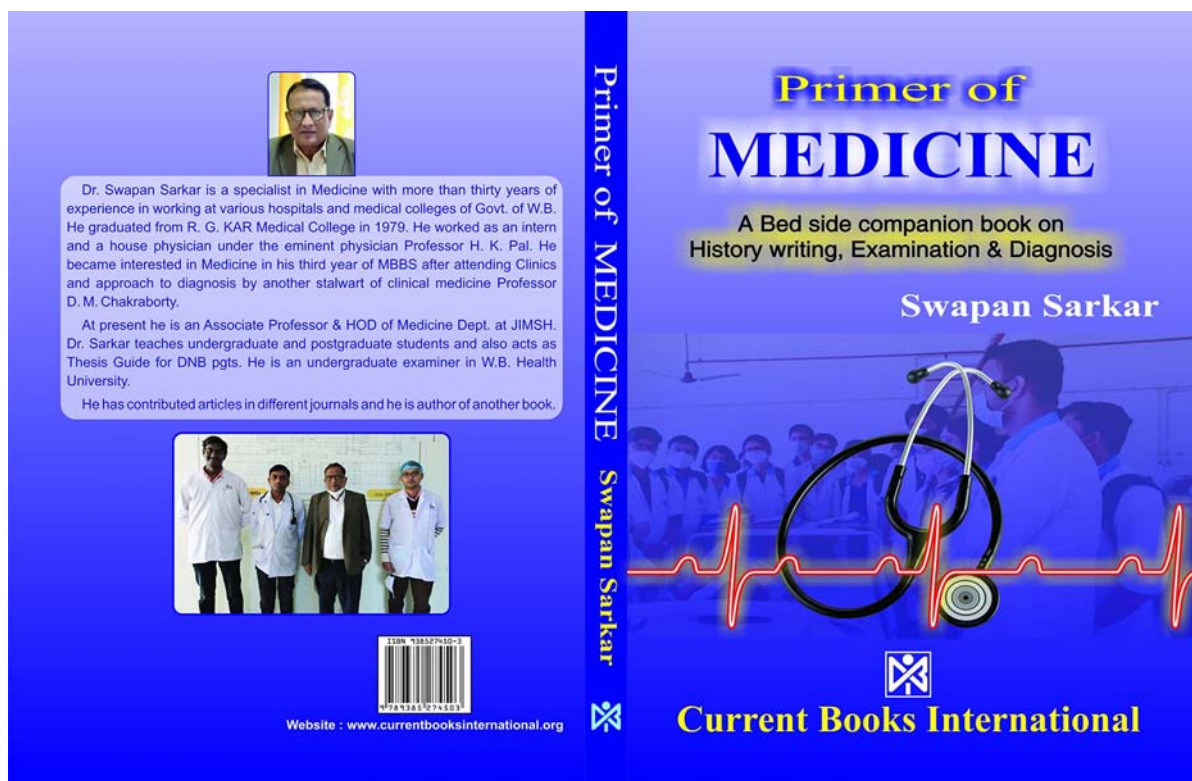


Fig 1 — ECG with raw data in rhythm strip at bottom; compare it LII in the 12 lead ecg which is linked median



## Book Review



**Primer of MEDICINE Paperback by Dr Swapan Sarkar, 1<sup>st</sup> Edition, Publisher : Current Books International, 34, Creek Row, Sealdah, Sealdah, Kolkata, West Bengal 700014, INDIA, Language : English, Paperback : 240 pages, ISBN-10 : 9385274503, ISBN-13 : 978-9385274503, Reading age : 18 years and up, Item Weight : 400 g, Dimensions : 25 x 19 x 1.5 cm, Country of Origin : India, Publish Year : 2022, Price Paperback : Rs 350.00 .**

‘Primer of Medicine’ is a new book which is intended for undergraduate Medical students. It is a companion book intended for helping students write patients’ history at the bedside, and to examine and carry out relevant note-taking to arrive at a diagnosis.

The book has ten chapters, starting with History Taking, General Examination, Examination of GI, CVS, Respiratory and Nervous System, Endocrine, and Eye. Skin and ENT are also included, in brief, to cover the new curriculum. After each chapter a model case taking is mentioned.

Examples of OSCEs are given. Clinical notes, questions and answers with exercises are also included. At the end, pictures of different patients are presented to spot the diagnosis.

Altogether the book is a package for learning at the bedside and preparing for university examinations in Medicine.

It is a concise, well illustrated, and ready to read companion book that I **highly recommend** for the Undergraduate and Postgraduate students. The book is available online on [www.currentbooksinternational.org](http://www.currentbooksinternational.org) and [amazon.in](http://amazon.in).

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**Prof (Dr) Jyotirmoy Pal**

## Letters to the Editor

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

### JIMA — September, 2021

SIR — This study from the eastern part of India brings to notice a very important issue about the management of Crescentic Glomerulonephritis. It has mainly concentrated on clinical spectrum and outcome in non Lupus patients of crescentic glomerulonephritis. We all know that it is an age old convention of treating Lupus Glomerulonephritis with cyclophosphamide. Now the EUVAS protocol is venturing in non Lupus territory.

Also an important observation about the clinical spectrum has been put forward that a high degree of suspicion of RPGN should be there in all patients requiring dialysis when the disease duration is less than 3 months.

In this eastern part of India, Pauci immune Glomerulonephritis was found to be predominating as an etiology of non Lupus RPGN. It was found that worse outcomes were reported in case of IgA nephropathy and anti-GBM who developed RPGN.

In this study, the patients received IV Cyclophosphamide and it is heartening to know that 37.14% of the patient maintained remission either partial or complete. However I would like to share some concerns regarding this mode of therapy. Authors have mentioned that about 53% of total number of deaths was due to septicemia during the course of treatment. so how safe is cyclophosphamide in this scenario is a query.

Also because the number of anti-GBM disease (2) and IgA nephropathy (1) are so limited, outcome on these subsets of patients cannot be assessed and needs more evaluation.

The use of tunneled venous catheter is a very good option to prevent septicemia, though cost and poor infrastructure in the periphery may be an impediment.

Some studies are coming up where oral cyclophosphamide has been used and found to be non inferior, this may be a subject of future research.

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**Himadri Roy**  
**Barun Behari Das**

### Russian invasion of Ukraine and it's effect on Public Health

SIR — THE invasion of Ukraine by the Russians which started on the 24<sup>th</sup> February, 2022 has affected the public health of both the countries terribly with loss of multiple lives.

The healthcare facility of Ukraine has been affected catastrophically with this war specifically after what it has been through during the COVID-19 pandemic over the last two years. The depletion of public finances has further added oil to the fire of this crisis situation.

With an increase in casualties from the war, the demand of health care has risen steeply. However, the ability to meet these needs has been severely compromised due to the reckless destruction of the infrastructure, shortage of all medical supplies- even oxygen and displacement of healthcare workers. The healthcare workers are being forced to shift their vital works underground. Their maternity and paediatric wards have been shifted into the underground bomb shelters for safety.

The healthcare facilities of the nearby countries who are helping the refugees, like Poland, are also suffering as a result of this war. Not only has there been an increase in number of casualties due to the war but an increase in COVID-19 and other infectious disease like HIV, tuberculosis, enteric fever among the refugees- who are fleeing the country in over-crowded unsanitary conditions. These unwell refugees are in dire need of medical attention from the nearby countries who are themselves striving to survive from crumbling healthcare facilities in the post COVID era.

Apart from physical health, the mental health of the survivors and the refugees has also been gravely affected by the Russian invasion. Families have been torn apart from their roots with no hopes of meeting again.

I, much like the rest of the world, wish for this war to come to an end with the retreat of the Russian forces in order to avoid any further casualties and loss of lives of civilians.

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**Tanuka Mandal**

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Dr. Tanu Raj Sirohi  
Internal Medicine  
Uttar Pradesh



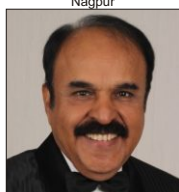
Dr V G Pradeep Kumar  
Neurologist  
Kozhikode, Kerala



Dr V Amuthan Emeritus  
Cardiologist  
Tamil Nadu



Dr V Mohanan Nair  
Public Health  
Ananthapuri



Dr A Muruganathan  
Medicine  
Tamil Nadu



Dr Alok Pandit  
Neurologist  
Kolkata



Dr Deepraj Bhandarkar  
Minimal Access Surgeon  
Mumbai



Dr C Daniela  
Radiologist  
Shillong, Meghalaya



Dr Anju Grewal  
Anaesthesiologist  
Punjab



Dr Vikram Kate  
Gastro Surgeon  
Puducherry



Dr Om Tantia  
Bariatric Surgeon  
Kolkata



Dr Avijit Hazra  
Pharmacology  
Kolkata



Dr Yim Heng Boon  
Hepatologist  
Singapore



Dr Gautamananda Roy  
Acute & Stroke Medicine  
UK



Dr Colin Robertson  
A&E Medicine  
UK



Dr Shoehal M Arafat  
Medicine  
Bangladesh



Dr Narimantas E Samalavicius  
Robotic Surgeon  
Lithuania



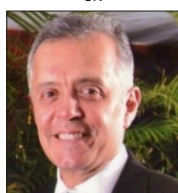
Prof Roman Jaeschke  
Medicine  
Canada



Dr Partha Sarathi Roy  
Neurologist  
UK



Dr Fazila TN Malik  
Cardiologist  
Dhaka Bangladesh



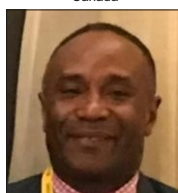
Dr. Ricardo Escalante  
Colorectal Surgeon  
Venezuelan



Dr SM Mostafa Zaman  
Cardiologist  
Dhaka, Bangladesh



Dr Serene Perkins  
Chief Medical Officer  
USA



Dr JWJ Nunoo - Mensah,  
Colorectal Surgeon  
London



Dr Aminur Rahman  
Neurologist  
Dhaka, Bangladesh





Release of BIMACON-2022 Souvenir



National President and Jt. Secretary, Hqs being received at Calcutta Airport by Prof Jyotirmoy Pal, Hony Secretary, JIMA



Past National President, Dr Santanu Sen, MP addressing BIMACON-2022



JIMA Volume for the year 2021 being handed over to National President by Prof Sujoy Ghosh, Hony Editor, JIMA



Felicitations of Janab Firhad Hakim, Mayor of Calcutta



Felicitations of National President at JIMA



IMA Jharkhand State Conference




World Kidney Day being observed by IMA Hqs



Mr Goutam Das retires after serving JIMA for long 41 years














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 Bioequivalent to the Leading Brand	Outstanding Quality and Accurate Dosing
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 Patented Blenders	Content Uniformity in Each Tablet Offers Batch to Batch Consistency
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 Pack Labels Matching Tablet Colour	Ease of Identification Ensures Better Patient Compliance



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