

# C O N T E N T S

**Journal, Indian Academy of Clinical Medicine • Vol. 18, Number 4, October-December, 2017**

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# JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

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for the

**Indian Association of Clinical Medicine**

*Headquarters :*

Post-Graduate Department of Medicine, Sarojini Naidu Medical College, Mahatma Gandhi Road, Agra - 282 002 (U.P.)

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4/19 B, Jangpura B, New Delhi - 110 014

Tel.: (011) 23361252

**E-mail: [iacmjournal@gmail.com](mailto:iacmjournal@gmail.com)**

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

**Indexed in Scopus, IndMED**

**Listed in UGC Approved List of Journals**

**“Bibliographic details of the journal available in ICMR-NIC’s database – IndMED (<http://indmed.nic.in>). Full-text of articles (from 2000 onwards) available on medIND database (<http://medind.nic.in>).”**

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Published by Dr. MPS Chawla  
for and on behalf of the Indian Association of Clinical Medicine  
from 4/19 B, Jangpura B, New Delhi - 110 014  
and printed by him at Sumit Advertising, 2 DLF (Part) Industrial Area, Moti Nagar, New Delhi - 110 015.



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## Coronary Artery Blocks have Little to do with Heart Attacks

BM Hegde\*

***"She smiled, and there it was again, that aching pressure in his chest. Love, or a heart attack. Kind of the same thing!"***

– Kristan Higgins.

Less than 30% of the heart attack related coronary arteries are more than 50% blocked wrote Valentine Fuster from New York years ago. Now comes an extensive study from America\* (our Indian intellectuals believe only such studies) which totally dissociates coronary arteries from heart attacks. Routine coronary angiograms were done on a cohort of men. Those with single vessel disease were left alone but it was predicted that sooner or later they will get a heart attack from that vessel block. Follow-up showed that some of them did get an infarct (heart attack) but ***never in the area of the heart supplied by that single blocked vessel!*** The infarct was always elsewhere. Most doctors are already aware of the normal coronary artery angina (NCA angina).

### Then how do people get relief from chest pain after coronary interventions?

Coronary interventions have been shown to be just placebos, but their fallouts are real, though. Having paid all your life's savings and having that much of faith in your doctor must get you relief for sure! Actually when we tell the patient that s/he has a 100% blocked vessel we fail to tell him why did that not give him a heart attack in the first place? There is the secret of nature's way of protecting us to the extent possible. The so called block did not happen on the day of the angiogram or a day earlier. ***It would have taken years to build up.*** Concurrently nature tries to develop collaterals which are normal vessels which connect other normal coronaries to supply blood to the needy area. This fact is hidden from the anxious patients lest s/he should slip out of our hands! In fact, in most cases nature does such effective bypass long before the doctor does his cosmetic interventions. I must quote a patient of mine here. This pleasant elderly man saw

me for his exertional chest pain which got better with lifestyle modification and drugs. His children were all in the US. They insisted on an angiogram which showed all the coronaries fully blocked but I saw so much natural bypass with collaterals that I felt he did not need any interventions. His children did not trust this village doctor and took him to the US to Mayo clinic where the cardiologist had a look at the angiogram and agreed with my assessment. The man is alive now after 35 years aged 94 fit as a fiddle! In between he had three surgeries for the cancer of his tongue. Death has very little to do with disease; and is independent of the latter!

### What, then, brings on a heart attack?

It is always the mind that does it. We are endowed with our protective autonomic nervous system which is not under our voluntary control. There are two parts of it, the sympathetic 'fight, flight' mode and the parasympathetic 'tranquillity' mode. A child has a clean mind filled with altruism and no negative feelings towards anyone. The child's heart in the parasympathetic mode which can be detected by its heart rate dependence on breathing which is very tranquil and diaphragmatic. (Belly button breathing) Child's heart goes faster when it breathes in and slower during breathing out. This is called heart rate variability (HRV). As we grow older and acquire negative thoughts like greed, jealousy, hatred, and anger, we go away from this mode. Our HRV keeps reducing making us more and more regular heart. The day the heart becomes totally regular in the sympathetic mode we are liable to get a heart attack!

To keep the heart healthy does not go after the innocent coronary arteries and cholesterol, etc., but try and keep a child's heart into adulthood and old age filled with universal compassion. Exception to every rule should be there to prove the rule. Like smoking causes cancer is almost a rule but some non-smokers also get cancer and some smokers like Winston Churchill did not get cancer! Exceptions only

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prove the rule. Mind is the boss in illnesses and keeping our mind in the parasympathetic tranquillity mode should be our priority to keep our heart healthy and to keep diseases away. In a cohort of 100 patients who were asked to have urgent bypass surgery (without which they were told that they may not live) we have been able to avoid surgery and make them

fit again by improving their HRV by yoga and pranaayaama and change in their lifestyle. This paper has been published in the API journal and was done along with Yoga centre in Santa Cruz, Mumbai.

*\*Sroka K et al. Heart rate variability in myocardial ischaemia during daily life. J Electrocardiol 1997; 30: 45-56.*

# Avas

# Study of Respiratory Muscle Strength in Patients of Liver Cirrhosis and its Correlation with Severity of Liver Disease

Priyanka Singh\*, Geeta Kampani\*\*, MK Sen\*\*\*, SP Singh\*\*\*\*

## Abstract

**Background:** *Dyspnoea is an important manifestation in patients of liver cirrhosis and has several causes. Respiratory muscle weakness contributes significantly to dyspnoea in patients of cirrhosis and is responsible for increased post-transplant mortality.*

**Aims:** *Study of respiratory muscle strength in patients of liver cirrhosis and its correlation with severity of liver disease.*

**Methods:** *It was a cross-sectional study conducted in VMMC and Safdarjung Hospital, New Delhi. It was conducted on 50 patients of liver cirrhosis. Dyspnoea was rated according to the modified Medical Research Council (mMRC) 5-point scale. Liver disease severity was assessed according to the Model for end-stage liver disease (MELD). Pulmonary function tests, maximum static expiratory (Pemax) and inspiratory (Pimax) mouth pressures were measured. Respiratory muscle strength (RMS) was calculated from Pimax and Pemax values.*

**Results:** *Forty nine (98%) of 50 patients aged (mean  $\pm$  SD)  $42.24 \pm 10.74$  years reported various degrees of chronic dyspnoea (mMRC), ranging from 1 to 4, with a mean value of  $2.06 \pm 0.62$ . MELD score was  $20.24 \pm 6.54$ . Pemax, per cent of predicted (%pred) was  $65.3 \pm 13$ , Pimax, %pred was  $59.76 \pm 14$ , and RMS, %pred was  $65.64 \pm 11$ . These pressures were below the normal limits in 39 (78%), 41 (82%), and 40 (80%) patients, respectively. Furthermore, comparing the subgroups of ascites to non-ascites patients, all respiratory muscle indices measured were found significantly decreased in ascites patients. Patients with ascites also had a significantly worse MELD score compared to non-ascites ones ( $P < 0.0001$ ) and had a higher mMRC value ( $P = 0.0003$ ). Significant correlations were found between chronic dyspnoea and respiratory muscle function indices in all patients. mMRC score was significantly correlated with Pemax, Pimax, and RMS ( $r = -0.398, P = 0.0042$ ;  $r = -0.453, P = 0.001$ ;  $r = -0.419, P = 0.0025$ , respectively). Similar results were found for the relationship between mMRC vs MELD score, and MELD score vs respiratory muscle strength indices. In all patients the sole predictor of mMRC score was MELD ( $P = 0.009$ ).*

**Conclusion:** *We conclude that respiratory muscle strength is decreased in Indian patients of liver cirrhosis and is inversely correlated with the severity of liver disease. The prevalence of chronic dyspnoea is 98% in end-stage liver disease. The mMRC score correlates negatively with respiratory muscle strength. It can be considered as a part of investigations done in patients planned for liver transplantation.*

**Key words:** *Cirrhosis, hypoxaemia, dyspnoea, Pimax, Pemax, RMS, MELD, mMRC.*

## Introduction

Liver cirrhosis and its complications are a leading cause of death among adults. Globally, liver cirrhosis deaths increased from around 6,76,000 in 1980 to over 1.3 million in 2015 (95% uncertainty interval: 1.2 million to 1.4 million)<sup>1</sup>.

Cirrhosis is a worldwide problem that is associated with a substantial economic burden. In the United States the national cost for treatment in 2008 ranged from \$14 million to \$2 billion, depending on disease aetiology.

Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver disease are the main causes of cirrhosis, but cost-effective preventive strategies are only available for HBV infection. In addition, liver transplantation (the only cure for cirrhosis) continues to consume substantial economic resources, despite a recent

reduction in overall cost.

Liver transplantation has become the therapeutic option of choice for patients with end-stage liver disease. These patients are usually characterised by tiredness, chronic fatigue, protein wasting and loss of muscle mass. The loss of muscle mass is of both peripheral, and that of respiratory muscle.

Liver plays a central role in health and homeostasis and thus, the diseased liver leads to many deleterious effects on multiple organ systems, including the pulmonary system<sup>2</sup>.

Pulmonary symptoms and abnormalities occur commonly in patients with liver cirrhosis regardless of aetiology. Arterial blood gas and pulmonary function test abnormalities are common and found in 45% - 50% of cirrhotic patients<sup>3</sup>.

Chronic dyspnoea is the major pulmonary symptom in patients

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with liver cirrhosis. 70% of cirrhotic patients evaluated for liver transplantation complain of dyspnoea<sup>4</sup>. Mild hypoxia is seen in approximately one-third of patients of chronic liver disease. Presence of hypoxaemia modifies the line of management and worsens the prognosis of the disease<sup>5</sup>.

There are many factors implicated in pathogenesis of hypoxaemia in cirrhosis such as ascites, hepatopulmonary syndrome, increased closing volume, low albumin levels, anaemia, respiratory muscle weakness, and extreme hepatomegaly but none of them have been proven as the sole reason. There is no simple mechanism to explain the association between liver disease and hypoxaemia and probably, many factors have a role in pathogenesis<sup>6</sup>.

The severity of liver disease is assessed according to the model for end-stage liver disease (MELD, United network for organ sharing modification). The united network for organ sharing and Euro transplant currently use MELD score for prioritizing patient allocation for liver transplantation, instead of the older Child-Pugh Score<sup>7</sup>.

The level of muscle weakness is estimated by the measurement of maximum inspiratory (Pimax) and maximum expiratory (Pemax) pressures which are useful to evaluate pulmonary functions and estimate lung risk in liver cirrhosis<sup>8</sup>.

However, there are very few Indian studies on respiratory muscle strength (RMS) in patients of liver cirrhosis, its correlation with severity of dyspnoea and with severity of liver disease. It is important to study this as it has great influence on post-transplant morbidity and mortality in patients of chronic liver disease.

With this background, we sought to analyse respiratory muscle strength in patients with liver cirrhosis and study its correlation with the severity of dyspnoea and severity of liver disease.

## Material and method

This hospital-based, cross-sectional study was conducted on 50 patients with liver cirrhosis recruited from the OPD of General Medicine and Gastroenterology clinic of VMMC and Safdarjung Hospital, New Delhi.

Each patient was subjected to detailed history and examination of past records with special emphasis on records of any intrinsic pulmonary disease (parenchymal or pleural disease), cardiovascular disease and other co-morbid condition. Patients in hepatic encephalopathy, with intrinsic parenchymal pulmonary disease (COAD, Bronchial Asthma, Pneumonia, ILD), pleural effusion, cardiovascular diseases such as congestive heart failure, neuromuscular disease, preterminal stage of illness, were excluded from the study.

Diagnosis of liver cirrhosis was based on:

1. Clinical findings
2. Biochemical findings (low serum albumin, AST:ALT ratio > 1)
3. Imaging findings (USG finding<sup>9</sup> - heterogenous echotexture of liver with irregular outline, altered liver size and presence of portosystemic collaterals).

All routine investigations along with coagulation profile, and kidney function test were done. Spirometric examination was done using Medisoft Spiroair Model Body Box 5,500 Spirometer and FEV1 (Forced expiratory volume in the first second), FVC (Forced vital capacity), FEV1/FVC, flow-volume loop, and volume-time loop were measured.

Respiratory muscle strength was assessed by using Micro RPM and Pemax, Pimax were recorded, and RMS was calculated as arithmetic mean of Pemax and Pimax<sup>10</sup>.

MELD score, used to assess the severity of liver disease was calculated as, MELD score =  $3.78 \times \log$  serum bilirubin (mg/dl) +  $11.20 \times \log$  INR +  $9.57 \times \log$  serum creatinine (mg/dl) + 6.43 (constant for liver disease)<sup>7</sup>.

mMRC 5 point scale was used to rate chronic dyspnoea<sup>11</sup>.

## Statistical analysis

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean  $\pm$  SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used. Quantitative variables were compared using Independent T-test/Mann whitney test (for non-parametric data) between two groups. Spearman rank correlation co-efficient (as the data was non-parametric) was used to assess the association of various quantitative parameters. Univariate and multivariate linear regression was used to assess the significant factors for predicting mMRC. A p value of < 0.05 was considered statistically significant.

## Observations and results

The study was conducted on 50 patients of liver cirrhosis after fulfilling the inclusion and exclusion criteria. The mean age of the patients was 42.24 ( $\pm$  10.74) years. Majority of patients were in the age group of 41 - 50 years and very few patients were in  $\leq$  30 years. Out of 50 patients of cirrhosis, 37 (74%) patients were male and 13 (26%) patients were female.

Alcohol was the most common cause of liver cirrhosis in our study with 27 (54%) patients. 9 (18%) patients were hepatitis C related cirrhosis, while 7 (14%) patients were hepatitis B related, and the cause was undetermined in 7 (14%) patients.

Among the study population, mean MELD score was  $20.24 \pm 6.54$ . Mean mMRC scale was  $2.06 \pm 0.62$ . 49 (98%) of 50 patients had dyspnoea. Grade 2 dyspnoea was reported in 37 (74%) patients, grade 3 in 7 (14%) patients, grade 1 in 4 (8%) patients while 1 (2%) patient had grade 4 dyspnoea. ABG analysis revealed hypoxaemia in 39 (78%) patients.

In the study population, mean Pimax was  $51.24 \pm 9.96$ , mean Pemax was  $79.7 \pm 13.77$  and mean RMS was  $65.64 \pm 11.58$ . 41 (82%) patients had low Pimax, 39 (78%) had low Pemax, and 40 (80%) patients had low RMS (< 80% predicted) (Table I).

**Table I: Basic parameters of patients.**

Parameter	Results
Age	42.24 ( $\pm 10.74$ ) years
Sex	37 (74%) Male 13 (26%) Female
Serum bilirubin	3.97 $\pm$ 3.81
Serum creatinine	1.63 $\pm$ 0.67
INR	1.75 $\pm$ 0.42
MELD score	20.24 $\pm$ 6.54
Albumin	2.57 $\pm$ 0.51
Ascites	Absent 13 (26%) Present 37 (74%)
PaO <sub>2</sub>	70.98 $\pm$ 8.27 Low PaO <sub>2</sub> = 39 Normal PaO <sub>2</sub> = 11
PaCO <sub>2</sub>	39.6 $\pm$ 6.33 Low PaCO <sub>2</sub> = 14 Normal PaCO <sub>2</sub> = 36
mMRC Scale	2.06 $\pm$ 0.62
FEV1	59.82 $\pm$ 19.28
FVC	66.36 $\pm$ 19
FEV1/FVC	94.48 $\pm$ 10.84
Pimax	51.24 $\pm$ 9.96
Pimax (% predicted)	59.76 $\pm$ 14.3 [Low (< 80%) = 41 Patients]
Pemax	79.7 $\pm$ 13.77
Pemax (% predicted)	65.3 $\pm$ 13.07 [Low (< 80%) = 39 Patients]
RMS	65.64 $\pm$ 11.58
RMS (% predicted)	62.78 $\pm$ 13.55 [Low (< 80%) = 40 Patients]

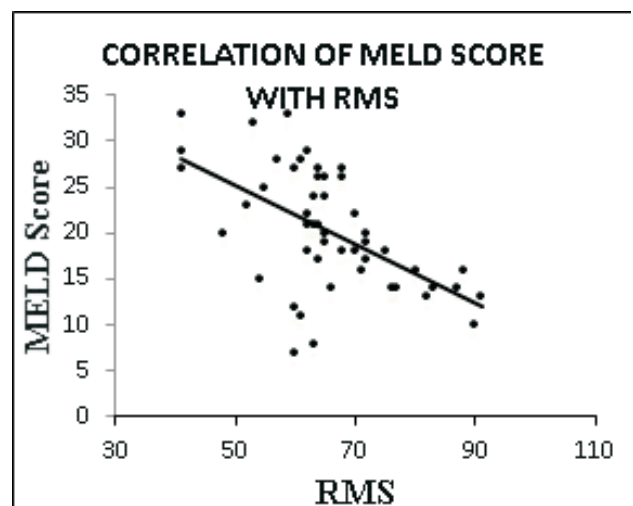
On comparing patients with ascites (n = 37) and those

without ascites (n = 13), it was observed that patients with ascites had lower PaO<sub>2</sub> ( $68.08 \pm 6.74$  vs  $79.23 \pm 6.58$ , p < 0.0001), lower Pemax ( $76.27 \pm 12.22$  vs  $89.46 \pm 13.68$ , p = 0.007), lower Pimax ( $48.57 \pm 9.31$  vs  $58.85 \pm 7.77$ , p = 0.001), and worse RMS ( $62.57 \pm 10.38$  vs  $74.39 \pm 10.6$ , p = 0.001). Ascitic patients were more dyspneic than non ascitic patients (mMRC  $2.24 \pm 0.49$  vs  $1.54 \pm 0.66$ , p = 0.0003). Also ascitic patients had worse MELD score compared to non ascitic patients ( $22.4 \pm 5.95$  vs  $14.08 \pm 3.57$ , p < 0.0001) (Table II).

**Table II: Comparison of different variables between ascitic and non ascitic group.**

Parameter	Ascitic (n = 37)	Non ascitic (n = 13)	P value
MELD	22.4 $\pm$ 5.95	14.08 $\pm$ 3.57	< 0.0001
mMRC	2.24 $\pm$ 0.49	1.54 $\pm$ 0.66	0.0003
PaO <sub>2</sub>	68.08 $\pm$ 6.74	79.23 $\pm$ 6.58	< 0.0001
Pemax	76.27 $\pm$ 12.22	89.46 $\pm$ 13.68	0.007
Pimax	48.57 $\pm$ 9.31	58.85 $\pm$ 7.77	0.001
RMS	62.57 $\pm$ 10.38	74.39 $\pm$ 10.6	0.001

Concerning the interrelationship between respiratory muscle strength, dyspnoea, hypoxaemia, and severity of liver disease, we found that MELD score correlated negatively with Pemax (r = -0.432, p = 0.0017), Pimax (r = -0.628, p = 0.0001), RMS (r = -0.537, p = 0.0001) (Fig. 1) and with PaO<sub>2</sub> with Pearson's correlation factor r = -0.849 and p value of < 0.0001 while it correlated positively with mMRC scale with Pearson's correlation factor r = 0.678 and p value of < 0.0001 (Fig. 2). PaO<sub>2</sub> correlated positively with Pemax (r = 0.584, p < 0.0001), Pimax (r = 0.378, p = 0.0068), RMS (r = 0.483, p = 0.0004) and negatively with mMRC dyspnoea score with Pearson's correlation factor r = -0.584 and p



**Fig. 1: Correlation of MELD score with RMS.**

value of  $< 0.0001$ . mMRC dyspnoea grade correlated negatively with RMS ( $r = -0.419$ ,  $p = 0.0025$ ), Pemax ( $r = -0.398$ ,  $p = 0.0042$ ), Pimax ( $r = -0.453$ ,  $p = 0.001$ ) (Fig. 3).

In univariate regression, all factors were significant predictors of mMRC score, but after adjusting for confounding factors, in multivariate regression only MELD score was the significant predictor with p value of 0.009.

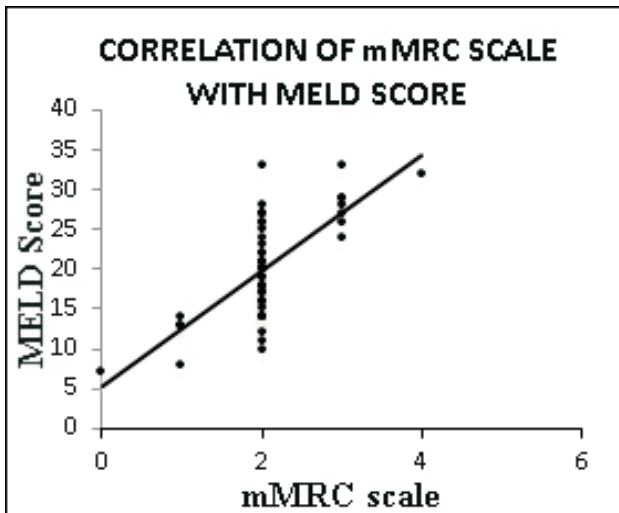


Fig. 2: Correlation of mMRC with MELD.

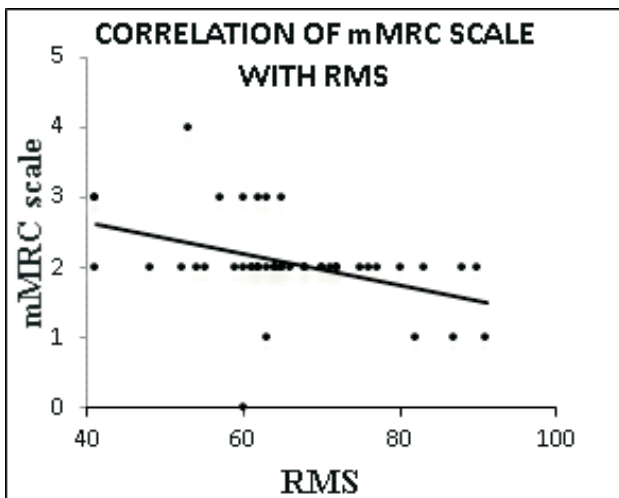


Fig. 3: Correlation of mMRC with RMS.

## Discussion

Cirrhosis of liver is characterised by pathological features which consist of the development of fibrosis, to the point, that there is architectural distortion with the formation of regenerative nodules irrespective of the cause. Dyspnoea and pulmonary complications are common in patients of liver cirrhosis and also increase post-transplant morbidity and mortality.

In our study, mean MELD score was  $20.24 \pm 6.54$ . 41 (82%) patients had low Pimax, 39 (78%) had low Pemax, and 40 (80%) patients had low RMS ( $< 80\%$  predicted). MELD score correlated negatively with Pemax, Pimax, RMS ( $r = -0.432$ ,  $p = 0.0017$ ;  $r = -0.628$ ,  $p = 0.0001$ ;  $r = -0.537$ ,  $p = 0.0001$  respectively). Similar results have been documented in previous studies.

Sameh Ahmed *et al*<sup>3</sup>, evaluated respiratory muscle strength, occurrence of hypoxaemia and chronic dyspnoea and their interrelationship in 100 cirrhotic patients. Patients mean MELD score was  $16.9 \pm 5.23$ . 39 (39%) patients had low Pimax, 35 (35%) patients had low Pemax and 37 (37%) patients had low RMS ( $< 80\%$  predicted). MELD score was correlated negatively with RMS ( $r = 0.824$ ,  $p < 0.001$ ).

Georgios Kaltsakas *et al*<sup>11</sup>, also evaluated patients with end-stage liver disease awaiting liver transplantation. Mean MELD score was  $14 \pm 6$ . Pemax, Pimax, and RMS were below the normal limits in 30%, 38%, and 35% patients, respectively. Respiratory muscle strength indices are inversely related to MELD score ( $p < 0.001$ ).

Among our patients, 98% (49 out of 50) of patients had dyspnoea. mMRC dyspnoea grade correlated negatively with RMS, Pemax, Pimax ( $r = -0.419$ ,  $p = 0.0025$ ;  $r = -0.398$ ,  $p = 0.0042$ ;  $r = -0.453$ ,  $p = 0.001$  respectively). A study by Kaltsakas *et al*<sup>11</sup> concluded that, dyspnoea is common (88%) in patients with end-stage liver disease. mMRC scale was significantly correlated negatively with RMS ( $p < 0.001$ ).

In our study, significant positive correlation was observed between mMRC and MELD score ( $r = 0.678$ ,  $p < 0.0001$ ). Sameh Ahmed *et al*<sup>3</sup>, concluded that chronic dyspnoea is prevalent in patients of liver cirrhosis and correlates positively with severity of liver disease.

Georgios Kaltsakas *et al*<sup>11</sup>, also found a positive correlation between severity of dyspnoea and MELD score ( $r = 0.43$ ;  $p < 0.01$ ).

In our study population, ABG analysis revealed hypoxaemia in 39 (78%) patients. mMRC dyspnoea scale and MELD score correlated negatively with  $paO_2$ , ( $r = -0.584$ ,  $p < 0.0001$ ;  $r = -0.849$ ,  $P < 0.0001$  respectively).  $PaO_2$  correlated positively with Pemax, Pimax, RMS ( $r = 0.584$ ,  $p < 0.0001$ ;  $r = 0.378$ ,  $p = 0.0068$ ;  $r = 0.483$ ,  $p = 0.0004$  respectively).

Sameh Ahmed *et al*<sup>3</sup>, also observed hypoxaemia in 81% of cases, and 37% patients had low RMS. mMRC score correlated negatively with  $PaO_2$ , ( $p < 0.001$ ). MELD score correlated negatively with  $PaO_2$ , ( $p < 0.001$ ). They concluded that chronic dyspnoea and hypoxaemia are prevalent in patients of cirrhosis and correlates with respiratory muscle weakness and severity of liver disease.

In our study, ascites was present in 37 patients. Ascitic

patients had higher MELD score and were more dyspnoeic, also they had significantly decreased respiratory muscle strength suggesting that RMS correlates with severity of liver disease and severity of dyspnoea. Sameh Ahmed *et al*<sup>8</sup>, concluded that patients without ascites had significantly higher PaO<sub>2</sub>, Pimax, Pemax and RMS but lower mMRC values than ascitic patients. The RMS is less and severity of dyspnoea is more in patients of ascites than non-ascites patients, probably due to increased severity of liver disease.

Georgios Kaltsakas *et al*<sup>11</sup>, also concluded that all respiratory muscle indices were found significantly decreased in patients of ascites. Patients of ascites also had significantly worse MELD score compared to patients without ascites.

In our study, univariate regression analysis, showed that RMS, hypoxaemia, and MELD score, all factors were significant predictors of mMRC but after adjusting for confounding factors, in multivariate regression analysis only MELD score was the significant predictor with p value of 0.009. Severity of liver disease is the most significant predictor of dyspnoea in the patients of liver cirrhosis. Georgios Kaltsakas *et al*<sup>11</sup>, found that, on applying regression analysis, the sole predictor of mMRC score was RMS ( $r = -0.51$ ,  $P < 0.001$ ).

This disparity with our study could be due to a larger study population (68 patients) in the above study. Moreover, the mean MELD score of our study population was much higher ( $20.24 \pm 6.54$ ) than in the above study ( $14 \pm 6$ ).

Thus, we conclude that respiratory muscle strength is decreased in Indian patients of liver cirrhosis and is inversely correlated with the severity of liver disease. The mMRC score correlates negatively with respiratory muscle strength. It can be considered as a part of investigations done in

patients planned for liver transplantation.

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## Clinico-Pathological Profile of Typhoid Fever Patients in Delhi

Sanjay Raina\*, Ruchi Jain\*\*, Atindra Narayan\*\*\*, Sanjay Singhal\*\*\*\*

### Abstract

**Background:** Typhoid fever requires prompt diagnosis to avoid serious morbidity and mortality. Early diagnosis is still a challenge in developing countries and the clinical picture is not specific, leading to use of empiric antibiotic therapy.

**Methodology:** A retrospective study of culture proven cases of typhoid fever carried-out at a 600 bed teaching hospital in Delhi, India. The records of patients (age > 10 years) with a diagnosis of typhoid fever discharged from the Department of Medicine, between January 2012 and December 2012 were evaluated.

**Results:** A total of 88 patients were included. There was decreasing number of cases, with increasing age. The most common symptoms were headache, abdominal pain, loose stools and vomiting, and signs hepatosplenomegaly, only hepatomegaly, only splenomegaly. The lab findings were nonspecific. Typhidot test had low sensitivity. There was no significant difference in the mean time to defervescence in those with or without prior antibiotic therapy. Antibiotic treatment with combination of ceftriaxone and azithromycin was not superior to treatment with ceftriaxone alone.

**Conclusion:** Clinical features of typhoid fever were similar in our study to previous studies; however, non were sensitive or specific enough to enable a clinical diagnosis of typhoid fever. There is still need to find a sensitive and specific rapid test for reliable diagnosis of typhoid fever. Ceftriaxone is the cornerstone of antibiotic therapy for typhoid fever and adding azithromycin does not improve the outcome but adds to the cost of therapy.

**Key words:** Typhoid fever, hepatosplenomegaly, leucopenia, thrombocytopenia, typhidot test, ceftriaxone, azithromycin.

### Introduction

Typhoid fever a systemic infection, caused by *Salmonella typhi*, is a major cause of morbidity and mortality worldwide<sup>1</sup>. The acute illness is characterised by prolonged fever, headache, nausea, loss of appetite, and constipation or diarrhoea. Diagnosis, on clinical grounds alone, is difficult as symptoms are often non-specific and clinically non-distinguishable from other febrile illnesses.

Reports by the World Health Organisation reveal that about 21 million cases, and > 2,22,000 deaths, from typhoid fever occur annually throughout the world. Developing nations share the highest burden due to rapid population growth, increased urbanisation, and limited safe water and health systems<sup>2,3</sup>. In India, the disease is endemic with a variable incidence ranging from 102 to 2,219 per 1,00,000 population<sup>4</sup>.

The Widal test is commonly used in developing countries, but has variable sensitivity and specificity and problems in interpretation<sup>5,6</sup>. The rapid tests for typhoid, including typhidot test have recently come into vogue but have shown variable sensitivity and specificity<sup>7-10</sup>. Blood culture is the 'gold standard' for diagnosis and also gives information about antibiotic sensitivity of the isolate; however, it is

marred by cost, non-availability and prior administration of antibiotics<sup>11</sup>.

Therapy of enteric fever is becoming more challenging with time due to emergence of drug resistance. The beta-lactams (ceftriaxone and cefixime) are now being increasingly used, but have problems related to cost of therapy, a long time to defervescence and high rates of relapse. There have also been sporadic reports of high-level resistance to ceftriaxone in *S. typhi* and *S. paratyphi*<sup>12</sup>. Experience with new drugs such as azithromycin is, at present, scanty<sup>13</sup>.

There is lack of extensive local literature on this topic. Therefore, keeping and considering this in mind the present study was conducted at a tertiary care teaching hospital, that covers the susceptible population of Delhi. This study attempted to solve some of these pertinent clinical questions by studying the clinical and laboratory profile of patients with culture proven typhoid fever.

### Material and methods

This was a retrospective study of culture proven cases of Typhoid fever, carried out at a 600 bed teaching hospital in Delhi, India. After taking ethical committee approval, the records of all patients (age > 10 years) with a diagnosis of

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typhoid fever discharged from Department of Medicine of our hospital between January 2012 and December 2012 were evaluated. Only culture proven cases of typhoid fever were included in the study. Clinical, laboratory and treatment information was extracted from the medical records and analysed. The student's t-test was used to compare continuous variables and the Chi-square test was used to compare categorical variables. A p value of less than 0.05 was considered significant.

## Results

A total of 88 patients with culture proven diagnosis of typhoid fever during the period January 2012 to December 2012 were included in the study. 40 of the 88 patients were male and 48 were female. There was a decreasing number of cases, with increasing age (Fig. 1).

All patients had fever prior to admission; the median duration of fever prior to admission was 5.69 days, the range being 1 to 30 days. Chills were present in 53.4%. Headache, abdominal pain, loose stools and vomiting were the most common associated symptoms seen in 56.8%, 46.6%, 42% and 26.1% patients respectively. Eight (9%) patients complained of constipation. Hepatosplenomegaly was seen in 15.9% patients. Only hepatomegaly was seen in 4.5% while only splenomegaly was seen in 14.8% patients. Five patients had sinus bradycardia. One patient had Rose spots. Three patients gave history of typhoid fever in the past.

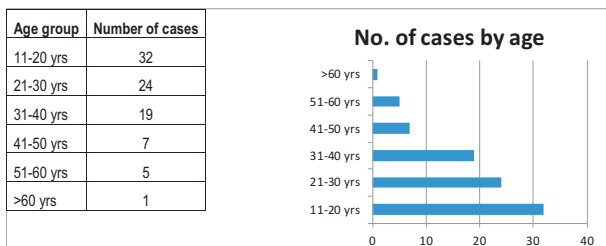


Fig. 1: Age distribution of typhoid fever.

Two patients suffered from mild clinical hepatitis (Table I).

**Table I: Commonly seen symptoms and signs in typhoid fever.**

Symptom	Number of cases	Sign	Number of cases
Headache	50	Hepatosplenomegaly	14
Abdominal pain	41	Splenomegaly alone	13
Loose stools	37	Hepatomegaly alone	4
Vomiting	23	Sinus bradycardia	5
Constipation	8	Rose spots	1

The mean white blood cell (WBC) count was 6,820/cumm with a range from 2,600/cumm to 14,400/cumm. WBC count within the normal range (4,000 - 11,000/cumm) was seen in 78.4%, of which 21.6% were in the low normal range (4,000 - 6,000/cumm). Leucopenia (WBC count < 4,000/cumm) was seen in 17% patients. Leucocytosis (WBC count > 11,000/cumm) was seen in only 4 patients. Absolute eosinopenia (0% eosinophils) was seen in 12.5% patients. The mean platelet count of the study patients was 2,33,705/cumm (range 80,000 to 4,50,000). Thrombocytopenia (platelet count < 1.5 lacs/cumm) was seen in 8%. Hyperbilirubinaemia (> 1 mg/dl) was seen in 13.6% while the ALT was elevated (> 60 IU/ml) in 5.7% patients. Typhid test was positive in 52 of 88 patients, (59%). 33 patients (37.5%) received antibiotics before being admitted to the hospital. IV ceftriaxone was the most common antibiotic used to treat patients in hospital; 57 of 88 patients (64.8%). A combination of IV ceftriaxone and oral azithromycin was used in 23 patients (26.1%). Three patients received cefixime, Three received amoxicillin-clavulanate combination and 1 patient, each, received ofloxacin and levofloxacin. The mean time to defervescence, defined as time period in days from the day of onset of the antibiotic treatment in the hospital to the disappearance of fever was calculated for various patient groups. The mean time to defervescence in the group of patients who had received antibiotics prior to admission was 3.77 days while in the patients who did not receive prior antibiotics was 3.96 days, (p = 0.2) which is not significant. The overall mean time to defervescence, when ceftriaxone alone was used as therapy, was 3.91 days. The mean time to defervescence in those patients who received a combination of ceftriaxone and azithromycin was 3.83 days, and did not differ significantly from those who received ceftriaxone alone (p = 0.11).

## Discussion

This study is a large, retrospective study on typhoid fever in the region. The distribution of cases clearly indicates decreasing incidence with increasing age, as has been reported in earlier studies<sup>13</sup>. Most of the clinical symptoms and signs reported by us are similar to those reported earlier; however, the relative occurrence of these is variable<sup>4,14,15</sup>. Bradycardia and constipation, considered to be salient features of typhoid fever were infrequent in our study<sup>4</sup>. Leucopenia was observed in 17% patients only, so cannot be relied upon as an indicator of typhoid fever<sup>16</sup>. Four patients in our study had leucocytosis which is unusual in typhoid. Absolute eosinopenia, considered a common finding by some studies (Deshmukh *et al* 71.4%) was seen only in 12.5% of our patients<sup>17</sup>. As many as 37.5% patients in our study received antibiotics, before being admitted to the hospital. Despite this, they were still culture positive.

The usual perception is that culture positivity falls dramatically with prior use of antibiotics<sup>14,17,18</sup> and often discourages us from sending blood cultures in patients with pyrexia. However, the results of our study indicate that blood cultures should be sent in suspected typhoid fever even if the patient is on antimicrobials. The mean fever clearance time, with ceftriaxone used as single therapy, observed in our study was 3.91 days, similar to other studies in literature. Surprisingly, prior antibiotic therapy was found to have no significant impact on the time to defervescence. There has been no comprehensive study evaluating the efficacy of combination therapy for typhoid fever. Results of our study indicate that combination therapy may not be superior to single drug therapy, as we did not observe any significant difference in the time to defervescence in those patients who received ceftriaxone alone, or in combination with azithromycin.

## Conclusion

Clinical features of typhoid fever have shown much variability in studies and the same was reflected in our study; also the features are not sensitive or specific enough to enable a clinical diagnosis of typhoid fever. Exotic features like relative bradycardia, Rose spots, and leukopenia do not contribute much to the diagnosis of typhoid fever. There is still a need to find a sensitive and specific rapid test for reliable diagnosis of typhoid fever. Ceftriaxone is the cornerstone of antibiotic therapy for typhoid fever and adding azithromycin to this does not improve the immediate outcome, but adds unnecessarily to the cost of therapy.

## Limitations

The main limitation of this study is its retrospective nature and that it was not protocol driven. Patients were receiving various antimicrobials singly or in combination for varying periods prior to hospitalisation, which could impact the time to defervescence. Also, the inability of the study to detect a difference in efficacy of antimicrobial regimens, chiefly single versus combination therapy, may be due to the small sample size.

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## Highly Sensitive C-Reactive Protein (hsCRP) and Microalbuminuria: New Markers of Cardiovascular Risk in Indian Patients of Type 2 Diabetes Mellitus

Rashmi Singh\*, Rajnish Singh\*\*, Pulin Kumar Gupta\*\*\*, RS Taneja\*\*, MPS Chawla\*\*, Neera Sharma\*\*\*\*, Mohd Ali\*

### Abstract

**Background:** Diabetics have a higher prevalence of Cardiovascular disease (CVD), which is attributed to newer emerging risk factors besides the conventional ones. We studied the levels of hsCRP and urinary albumin excretion (UAE) and its correlation with Carotid Intimal Medial Thickness (CIMT) - a surrogate marker of atherosclerosis, in type 2 diabetics.

**Methods:** It was a cross-sectional observational study conducted on 100 asymptomatic type 2 diabetics at PGIMER, Dr RML Hospital, New Delhi. Serum hsCRP and UAE were measured, besides the conventional risk factors for CVD. CIMT was measured by B-mode ultrasonography using a 3 MHz transducer. Multivariate regression analysis was done to find the independent association of hsCRP and UAE with CIMT.

**Results:** The study included 39 males and 61 females with mean age of  $54.63 \pm 11.65$  years. Mean duration of diabetes was  $5.9 \pm 1.3$  years with a range of 1 - 15 years and HbA1C of  $7.6\% \pm 0.9\%$ . The mean UAE was  $121.33 \pm 11.5$  mg/l with range from 10 mg/l to 480 mg/l. 52% of patients had microalbuminuria and 26% had macroalbuminuria (i.e., 78% had nephropathy). Mean hsCRP levels were  $3.76 \pm 0.41$  mg/l, ranging from 0.06 mg/l to 14.31 mg/l. 29 patients had hsCRP of 1 - 3 mg/l (intermediate risk) and 39 patients had hsCRP  $> 3$  mg/l (high risk as per AHA/ACC) implying that 68% patients had intermediate to high risk for CVD. hsCRP and UAE were significantly correlated with increasing age, Fasting Blood Sugar, HbA1C, duration of diabetes and high CIMT  $> 0.8$  mm ( $P < 0.01$ ). Mean CIMT was  $0.73 \pm 0.11$  mm. On multivariate analysis, hsCRP ( $p < 0.001$ ) and UAE ( $p < 0.016$ ) showed significant and independent association with CIMT. HbA1c, triglycides, LDL cholesterol, duration of diabetes and age also came out to be determinants of higher CIMT.

**Conclusion:** hsCRP and increased UAE are independent predictors of CVD in type 2 diabetes and should be considered new markers for CVD in addition to the conventional ones.

### Introduction

Diabetes patients have a high prevalence of CVD. Besides the conventional risk factors like age, sex, hypertension, Diabetes mellitus (DM), dyslipidaemia and obesity, studies are suggesting new risk factors. Studies have shown highly sensitive C-reactive protein (hsCRP) and urine albumin excretion (UAE) to be new markers of cardiovascular risk. hsCRP is closely related to low-grade vascular inflammation and microalbuminuria is considered to be a marker of endothelial dysfunction<sup>1</sup>. Atherothrombosis is increasingly interpreted as low-grade inflammatory disease of the vessel wall characterised by endothelial dysfunction and an increased transendothelial passage of leukocytes. Therefore, these features could be the pathogenic factors linking elevated hsCRP with increased risk for cardiovascular disease<sup>2</sup>. hsCRP is associated with subclinical epicardial coronary artery calcification in men and women<sup>3</sup> and is significantly ( $P < 0.005$ ) elevated in patients dying suddenly with severe coronary artery disease, both with and without acute coronary thrombosis. It also correlates with intensity

of immunohistochemical staining intensity and numbers of thin cap atheroma. Elevated levels of hsCRP in healthy patients have been found to be predictive of a first cardiac event and are useful in identifying patients at increased risk for a cardiac event<sup>4</sup>.

Microalbuminuria in type 1 and type 2 diabetes is usually accompanied by endothelial dysfunction with regard to the regulation of hemostasis, fibrinolysis, leukocyte adhesion, and nitric oxide synthesis. Several studies have shown that microalbuminuria, indeed, is associated with increased permeability to macromolecules in peripheral vascular beds<sup>5</sup>. In addition, microalbuminuria is associated with changes in regulation of vasomotor tone of peripheral vessels. Microalbuminuria is correlated with the development of atherosclerosis and the UAE begins to increase late in the atherosclerotic process.

CIMT is non invasive Doppler ultrasonography of both carotid arteries, and is an independent predictor of cardiovascular disease. It is the only non-invasive imaging test currently recommended by the American Heart Association as a

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surrogate marker of subclinical atherosclerosis. India is facing the dual epidemic of DM and CVD, higher than other ethnic populations. So, this study was aimed to see the association of hsCRP and microalbuminuria with CIMT, a marker of atherosclerosis, in Indian type 2 diabetic patients and thus, to infer whether hsCRP and microalbuminuria in type 2 diabetics can be included as new modifiable risk factors for atherosclerosis and subsequent cardiovascular disease.

## Material and methods

It was a cross sectional observational study conducted at PGIMER and Dr RML Hospital, New Delhi (a tertiary care hospital catering to a large population of north India). Study group included 100 consecutive type-2 diabetic patients, visiting the Medicine OPD of the Hospital, satisfying the inclusion and exclusion criteria, and after getting approval of institutional ethics committee.

Patients with a recent history of acute illness or inflammatory conditions, eGFR < 60 ml/min, serum SGPT > 3 times upper normal limit or serum bilirubin > 2 mg/dl, use of recent anti-inflammatory medications, history of rheumatological conditions, CAD, CVA and CKD were excluded. Detailed history of each subject was taken and clinical examination was done as per standard protocol. Age, sex and duration of diabetes were noted. Medication use data was obtained with particular focus on aspirin, statins, anti-diabetic and anti-hypertensive drugs, steroids and NSAIDs through questionnaire and pill reviews. Anthropometric examination included standing height, body weight and waist circumference. The patients were evaluated for CIMT by colour Doppler. Serum hsCRP level and UAE were measured, besides the conventional risk markers for atherosclerosis.

Proposed objective was to study hsCRP and albuminuria in type 2 diabetic patients and to find their association with CIMT (i.e., subclinical atherosclerosis). CIMT was measured by B-mode ultrasonography on Philips HD 11 by transducer L12 - 3 MHz by a single radiologist who was blind to the clinical characteristics of the patients. The mean CCA-IMT was defined as the mean of the right and the left CCAs calculated from 3 measurements on each side. CIMT  $\geq$  0.8 mm was considered abnormal.

The CRPHS immune turbidimetric assay was used for the quantitative determination of hsCRP in human serum on Roche automated clinical chemistry analysers. Cardiovascular risk was interpreted according to AHA/ACC guidelines with hsCRP < 1 mg/l = low risk, 1 - 3 mg/l = intermediate risk and > 3 mg/l = high risk<sup>6</sup>. Microalbuminuria (MAU) was defined as urinary albumin excretion rate between 20 - 200 mg/l in the first morning sample or 20 - 200  $\mu$ g/min in a timed overnight sample<sup>7</sup>. MAU was

detected by the HemoCue system (consisting of the HemoCue Urine Albumin Microcuvettes and the HemoCue Urine or Albumin 201 Analyser).

## Observations

Out of the total 100 patients enrolled, there were 39 males and 61 females. Mean duration of diabetes was  $5.9 \pm 1.3$  years with a range of 1 - 15 years. 15% of patients were smokers. The mean age of our study population was  $54.63 \pm 11.65$  years (range 25 - 80 years). Out of 100 patients, 79 were using Oral hypoglycaemic agents (OHA) only, whereas 21 were on Insulin  $\pm$  OHA treatment. About 45% of patients were taking statins. Equal numbers of patients were on aspirin. 44% of patients were hypertensive, and out of these, 80% were on dual agent anti-hypertensive drugs with good control. 50% of our patients were overweight (BMI 25 - 29.9 Kg/m<sup>2</sup>) and 47% were obese (BMI  $\geq$  30 Kg/m<sup>2</sup>), thus showing increased prevalence of obesity in study population. The mean fasting glucose was  $146 \pm 44$  mg/dl (range 102 - 190 mg/dl). The mean HbA1c was  $7.6 \pm 0.9\%$ . Values of HbA1c < 7% were found in only 25% patients, and 75% patients had HbA1c  $\geq$  7%. Estimated GFR (by MDRD equation) was  $90.58 \pm 20.37$  ml/min/1.73 m<sup>2</sup> with a range of 60 to 143 ml/min/1.73 m<sup>2</sup>.

The study population had mean HDL cholesterol of  $37.88 \pm 8.62$  mg/dl (16 - 59 mg/dl), mean triglyceride level of  $161.75 \pm 57.31$  mg/dl (93 - 358 mg/dl) and mean LDL cholesterol level of  $111.58 \pm 22.01$  mg/dl (71 - 155 mg/dl). Non-HDL cholesterol levels were  $132 \pm 31.31$  mg/dl (90 - 181 mg/dl). Less than 20% of our patients had their LDL/non-HDL cholesterol in good range, as advocated by NICE guidelines. The mean UAE was  $121.33 \pm 11.5$  mg/l with range of 10 to 480 mg/l. 52% of patients had microalbuminuria, 26% patients had macroalbuminuria, whereas 22% patients had no albuminuria. Thus, 78% of patients had nephropathy, i.e., microalbuminuria/macroalbuminuria.

Mean hsCRP level measured was  $3.76 \pm 0.41$  mg/l. Range was from 0.06 mg/l to 14.31 mg/l. There was no significant difference in serum hsCRP levels between males and females. There were 32 patients with serum hsCRP level < 1 mg/l, 29 patients with hsCRP of 1 - 3 mg/l and 39 patients with hsCRP > 3 mg/l (i.e., highest risk group). Thus, a large number of patients (68%) was in the higher risk group of hsCRP, as per ACC/AHA guidelines. In age group of 21 - 40 years, mean hsCRP level was  $0.87 \pm 0.55$  mg/l, in age group 41 - 60 years it was  $3.51 \pm 3.89$  mg/l, and in age group 61 - 80 years it was  $5.24 \pm 4.71$  mg/l. This shows a proportionate linear increase in hsCRP with increasing age ( $P < 0.0001$ ). There was a similar proportional increase in hsCRP with the duration of diabetes with highest hsCRP in patients with diabetes > 8 years ( $P < 0.001$ ). Significantly high hsCRP was

also seen in patients with higher HbA1c and FBS ( $P < 0.01$ ). Similarly, patients who were not on statins had higher hsCRP as compared to those on statin therapy ( $P < 0.05$ ).

The mean CIMT value was  $0.73 \pm 0.1119$  mm (range 0.51 - 1.1 mm). There were 31% patients who had CIMT  $> 0.8$  mm. On the basis of carotid intima media thickness, patients were divided in two groups:

Group 1: CIMT  $< 0.8$  mm

Group 2: CIMT  $\geq 0.8$  mm

Patients with CIMT  $\geq 0.8$  mm were considered to have increased cardiovascular risk<sup>8</sup>.

**Table I: Comparison of cardiovascular risk factors in both groups of patients.**

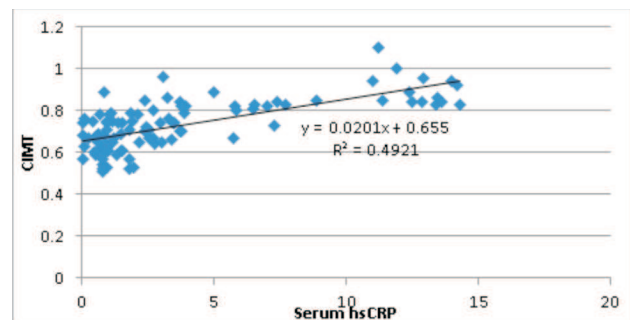
Variable	Cardiovascular risk		p-value
	CIMT $< 0.8$ mm	CIMT $\geq 0.8$ mm	
N	69	31	
Sex (M/F)	24/45	15/16	0.143
Age	$52.38 \pm 12.28$	$59.65 \pm 8.26$	<b>0.003</b>
Diabetes duration (years)	$4.99 \pm 3.67$	$7.44 \pm 5.03$	<b>0.007</b>
*OHAs only	35 (50.7%)	12 (38.7%)	0.185
*OHA + insulin	33 (47.8%)	18 (58.1%)	0.233
BMI (kg/m <sup>2</sup> )	$24.22 \pm 4.07$	$24.48 \pm 2.59$	0.738
*Smoking	9 (13%)	6 (19.4%)	0.297
*Statin user	28 (40.6%)	17 (54.8%)	0.134
*Aspirin user	28 (40.6%)	17 (54.8%)	0.134
*Anti-hypertensive user	26 (37.7%)	12 (38.7%)	0.547
Blood pressure (mm of Hg)			
Systolic	$132.68 \pm 10.67$	$132.75 \pm 9.43$	0.972
Diastolic	$80.41 \pm 8.60$	$81.56 \pm 9.08$	0.550
HbA1c (%)	$7.49 \pm 0.79$	$8.69 \pm 1.07$	<b><math>&lt; 0.001</math></b>
Triglycerides (mg/dl)	$147.93 \pm 35.49$	$192.52 \pm 81.07$	<b><math>&lt; 0.001</math></b>
HDL cholesterol (mg/dl)	$38.14 \pm 9.30$	$37.29 \pm 1.25$	0.612
LDL cholesterol (mg/dl)	$99.07 \pm 23.65$	$117.16 \pm 16.87$	0.049
eGFR (ml/min/1.73 m <sup>2</sup> )	$85.37 \pm 19.75$	$79.94 \pm 17.75$	0.06
UAE (mg/l)	$66.81 \pm 61.137$	$242.68 \pm 115.34$	<b>0.004</b>
hsCRP (mg/l)	$1.62 \pm 1.34$	$8.51 \pm 4.34$	<b>0.007</b>

CIMT was correlated with baseline characteristics and CVD risk factors along with hsCRP and UAE of patients. Mean hsCRP of group 1 was  $1.62 \pm 1.33$  and of group 2 was  $8.51 \pm 4.34$  mg/l. Mean UAE in all patients was  $121.25 \pm 70.36$  mg/l. UAE in group 1 was  $66.81 \pm 61.14$  and in group 2 was  $242.68 \pm 115.34$  mg/l. The statistical analysis should that patients with increased CIMT had significantly higher values of hsCRP ( $p$  value = 0.007) and UAE ( $p$  value = 0.004). Significant differences between these two groups were

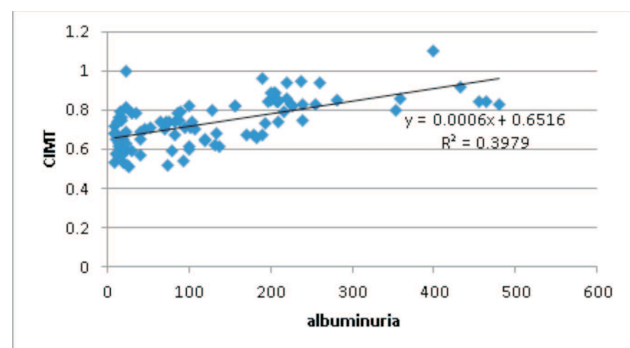
also found regarding HbA1c, triglyceride and LDL levels, duration of diabetes and age ( $P < 0.01$ ). Aspirin and statin use by patients did not show difference between the two groups. No correlation of CIMT was found with the use of antihypertensive drugs.

No significant association was seen between CIMT and eGFR, which means that MAU is perhaps a more valid and early marker of CAD (and also CKD) and, eGFR only, should not be relied upon in early stages of diabetes because it may be many years before eGFR decreases whereas MAU is seen even in stages of prediabetes. Also, eGFR is known to rise in early diabetes (stage of hyper filtration).

Simple univariate linear regression analysis was applied between CIMT as a dependant variable, and serum hsCRP and UAE as independent variables. It demonstrated that, CIMT has a significant correlation with serum hsCRP levels ( $r = 0.701$ ,  $r^2 = 0.492$ ,  $p$  value  $< 0.001$ ) and UAE ( $r = 0.631$ ,  $r^2 = 0.397$ ,  $p$  value  $< 0.001$ ). The means that 49% of total variation in hsCRP can be explained by the relationship between CIMT and hsCRP and similarly 39% of total variation in UAE can be explained by the relationship between CIMT and UAE level. In the multivariate regression analysis, serum hsCRP and UAE were found to be independently associated with CIMT, even after adjustment for multiple confounding factors like age, BMI, HbA1c, duration of diabetes, eGFR, lipids, blood pressure.



**Fig. A:** Scatter plot showing correlation between serum hsCRP and CIMT.



**Fig. B:** Scatter plot showing correlation between albuminuria and CIMT.

**Table II: Multivariate regression analysis with CIMT as dependent variable.**

Dependent variable	Independent variable	Standardised beta co-efficient	p-value
CIMT	Serum hsCRP	0.451	< 0.001
	Age	0.090	0.309
	Diabetes duration	-0.183	0.037
	BMI	-0.157	0.047
	HbA1c	0.195	0.049
	eGFR	-0.025	0.761
	TG	0.148	0.048
	HDL	0.039	0.607
	LDL	-0.197	0.024
	Urine albumin excretion	-0.237	0.016

The study showed a significant and independent association between serum hsCRP level and urine albumin excretion with CIMT, a marker of atherosclerosis.

## Discussion

hsCRP and albuminuria have shown good promise as new and early markers of CVD risk. The independent and positive relationship of these markers have already placed them amongst routine investigations, as part of annual examination for diabetes in some western countries. hsCRP > 1 mg/l in USA, is taken as an indirect maker of vascular inflammation and atherosclerosis. Similarly, MAU is considered as early marker of endothelial injury. CIMT, since long, has been recognised as a surrogate marker and non-invasive method of diagnosing atherosclerosis.

Our study showed that 68% of patients had hsCRP > 1 mg/l (i.e., high risk zone) and 78% of patients had nephropathy (MAU/overt albuminuria). This shows that around three-quarters of our patients had atherosclerotic process already under progress. This is a bit higher compared to other studies, which quote the prevalence of CVD in diabetes in the range of 50 - 60%, and it might be due to higher age group and poor diabetes control of our patients as well as lower aspirin and statin use. 31% of patients had CIMT > 0.8 mm and it correlated significantly and strongly with hsCRP and MAU. 61% of our patients were females (where we expect a low CIMT); however, even after that, 1 in every 3 patients had CVD. All these patients with high CIMT had high hsCRP and MAU and their predictive value was higher than conventional CVD risk markers in this study. Many western studies have also stated the same fact but the association in our study has come out to be much stronger.

Poor diabetes control as evident by mean HbA1c of 7.6% may also be a factor for high hsCRP and MAU. Another factor may be lesser use of statins and aspirin in our study population. Statins and aspirin are known to decrease hsCRP and MAU. Also, routine use of the commercially available fixed date combination in the form of aspirin 75 mg and atorvastatin 10 mg may be the responsible factor for low intensity statin therapy. International lipid guidelines have focused upon LDL cholesterol. Indian dyslipidaemia is much different where TG is disproportionately higher. TG is a major determinant in non-HDL cholesterol and many Indian studies have highlighted the importance of non-HDL over LDL cholesterol. In our study also, TG apart from LDL, was seen to correlate with increased CVD and so, TG reduction may be advised in diabetes patients with high hsCRP or MAU. CIMT, in our study, did not correlate with eGFR rather it had independent significant correlation with MAU. eGFR is even known to be higher in early stages of diabetes because of a process known as hyperfiltration, and it may take 5 - 10 years of slow renal injury to cause reduction in eGFR, and so it is a late marker of renal (or even cardiac) disease. This study again reinforces the fact that MAU should be a routine investigation in diabetes, not only for detecting nephropathy but also for picking up early atherosclerotic CVD.

However, this study had some limitations. This study was cross-sectional, and had no controls. This study had a small population which might result in type-II error or  $\beta$  error. Further, on the basis of this study, it is not possible to say whether hsCRP and/or UAE and atherosclerosis have a cause and effect relationship. This study did not analyse or compare patient data on the basis of presence or absence of CVD. Hence, larger, controlled prospective studies should be done to further establish this association.

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# Clinical Profile of Patients with Gestational Diabetes and Its Association with Maternal and Neonatal Morbidity and Mortality

Sanjay Raina\*, Ruchi Jain\*\*, Atindra Narayan\*\*\*

## Abstract

**Background:** Gestational diabetes mellitus (GDM) is a condition resulting from abnormal glucose metabolism during pregnancy which may adversely affect maternal and fetal health.

**Methodology:** To analyse incidence, risk factors and maternal and fetal outcome in women with GDM in a tertiary care centre. This is a prospective study recruiting 50 patients diagnosed with GDM and followed, till 2 weeks after delivery. Association of various risk factors with fetal and maternal complications was analysed.

**Results:** Incidence of GDM was observed to be 19.2%. Thirty three (66%) of these women were observed to have at least one risk factor. Polyhydramnios and urinary tract infection was more common in women age > 30 years ( $p$  value < 0.01); premature delivery in women with high BMI ( $p$  value < 0.05); hypoglycaemia in women with bad obstetric history ( $p$  value < 0.01); polyhydramnios and hyperbilirubinaemia in women with glycosuria ( $p$  value < 0.01). Family history of DM was not associated with statistically significant risk for development of complications. While analysing complications in women with or without at least one risk factor, incidence of neonatal hypoglycaemia was significantly higher in women with risk factor(s).

**Conclusion:** Dietary counselling, life style modification and appropriate timely institution of pharmacological therapy are critical to reduce the morbidity and mortality associated with GDM.

**Key words:** Gestational diabetes, fetal, maternal, diet, exercise.

## Introduction

Gestational diabetes mellitus (GDM) is abnormal glucose metabolism, which first develops during pregnancy. It is associated with many complications that can arise during the course of pregnancy, that may adversely affect health of mother and fetus<sup>1-2</sup>. Various studies have identified risk factors for development of GDM such as family history of diabetes, obesity, age more than 30 years, bad obstetric history and past history of large weight baby<sup>3-5</sup>. However, many Asians are detected to have GDM even in the absence of these risk factors. Institution of treatment at the right time and maintenance of tight glycaemic control can ensure marked reduction in morbidity and mortality associated with GDM<sup>6-8</sup>. Therefore, it becomes important that the physician, who is doing routine antenatal checkups realises the importance of this disease, identifies the high risk group, screens them and treats them at the earliest possible stage.

This study was undertaken to study the clinical profile of patients with gestational diabetes, maternal and fetal morbidity and mortality, and risk factors associated with these complications in a tertiary care centre.

## Material and methods

This is a prospective study that recruited 50 patients diagnosed with GDM to various OPD/IPD of a tertiary care centre in North India. All pregnant females in the antenatal clinic at 24 - 28 weeks of gestation were subjected to glucose challenge test (50 g of glucose). If blood sugar was > 140 mg% at 1 hour, they were subjected to oral glucose tolerance test (OGTT), and were labeled to have GDM if fasting blood glucose was > 95 mg% or post-prandial (2 hour) blood glucose was > 140 mg%<sup>9</sup>.

For all these patients, demographic profile, weight, body mass index (BMI), obstetric and familial diabetic history was recorded. Detailed counselling session was done for all these patients to increase their awareness about GDM, importance of diet control and its role in prevention of fetal and maternal complications. All the patients underwent dietary counselling, by a qualified dietician. If blood sugar was not optimally controlled with dietary modification, insulin was started. Various complications during antenatal period (abortion, polyhydramnios, pre-eclampsia, urinary tract infection); during delivery and perinatal period (type of delivery, prematurity, still birth, congenital malformation, macrosomia, birth weight)

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were recorded. Complications in new born baby such as hypoglycaemia, hypocalcaemia, respiratory distress syndrome, hyperbilirubinaemia, polycythaemia, thrombocytopenia, cardiomyopathy, necrotising enterocolitis, renal vein thrombosis were also recorded.

Categorical variables were described as frequency and percentage, and continuous variables as median and interquartile range (IQR). Strength of association for risk of occurrence of complication was performed using the Chi-square test with the following independent variables: Bad obstetric history (BOH), glycosuria, age more than 35 years, family history of diabetes, high BMI. The analyses were performed using SPSS software for Windows, version 16.0.

The study was carried out according to the institutional guidelines and was approved by the institutional review board/ethics committee.

## Results

During the study period, a total of 260 pregnant women were registered in the ante-natal clinic, and 50 were diagnosed to have GDM, with an incidence of 19.2%. Clinical profile of these patients is shown in Table I. Thirty three (66%) of these women were observed to have at least one risk factors (BOH, glycosuria, age more than 30 years, family history of diabetes, high BMI). The risk factors included high BMI 40% (20/50), family history of diabetes 32% (16/50), and age more than 30 years 16% (8/50), BOH 14% (7/50) and glycosuria 10% (5/50) respectively. Mode of delivery was normal vaginal in 23 (46%), cesarean section in 24 (48%), ventouse 1 (2%) and forceps assisted in 2 (4%) patients. Antenatal, perinatal and neonatal complications are shown in Table II. In assessment of risk factors for complications, polyhydramnios and urinary tract infection were more common in women of age > 30 years (p value < 0.01); premature delivery in women with high BMI (p value < 0.05); hypoglycaemia in women with BOH (p value < 0.01); polyhydramnios and hyperbilirubinaemia in women with glycosuria (p value < 0.01). Family history of diabetes was not associated with statistically significant risk for development of complications. While analysing complications in women with or without at least one risk factor, the incidence of neonatal hypoglycaemia was significantly higher in women with a risk factor(s).

## Discussion

This prospective, longitudinal study was carried out in a tertiary care centre in West Delhi. It caters to upper middle class population with a dedicated gynaecology, medicine and pediatric department. Incidence of GDM was observed to be 19.2%. In an other Indian study, Seshiah *et al* in 2010 prospectively observed the prevalence of GDM to be 13.4%

(n = 196) in 1,463 pregnant women by DIPSI criteria<sup>9</sup>. In 2013, Kalra *et al* found prevalence of GDM in Western Rajasthan, by DIPSI criteria, to be 6.6%<sup>10</sup>. Neelakandan *et al* (2012 - 2013; N = 1,106) found prevalence of GDM to be higher in elderly pregnant women<sup>11</sup>. Increased incidence in our study, may be attributed to higher proportion of women with high BMI, older age and predominantly urban population. GDM has been found to be more common in urban areas than in rural areas<sup>12</sup>.

**Table I: Clinical profile and treatment of study population.**

Characteristic	Number (%)
Age in years	
< 30 years	45 (90)
> 30 years	5 (10)
Risk factors	
Present	33 (66)
Absent	17 (34)
Fasting blood sugar (mg/dl)	
95 - 100	24 (48)
100 - 110	22 (44)
> 110	4 (8)
Post-prandial blood sugar (mg/dl)	
140 - 150	25 (50)
150 - 160	21 (42)
> 160	04 (8)
Treatment	
Diet modification	29 (58)
Insulin	21 (42)

**Table II: Ante natal, natal and post-natal complications in relation to maternal risk factors.**

	Risk factor Yes (N = 33)	Risk factor No (N = 17)	p value
<i>Ante natal</i>			
Polyhydramnios	5	0	0.15
Urinary tract infection	2	2	0.59
PIH	3	1	1
<i>Fetal</i>			
Prematurity	3	0	0.54
Still birth	1	0	1
Macrosomia	4	0	0.28
<i>Post-natal</i>			
Hypoglycaemia	12	1	0.03
RDS	1	1	1
Hypocalcaemia	1	0	1
Hyperbilirubinaemia	2	0	0.54

PIH: Pregnancy induced hypertension; RDS: Respiratory distress syndrome.

In our study, 66% women had one or more risk factors associated with GDM while in the study done by Vinita Das *et al*, it was found that 73.8% of the GDM patients had risk factors for development of GDM<sup>13</sup>. Martin AO Simpson *et al*, found that 62% of GDM patients had one or more risk factors for the development of GDM<sup>14</sup>. Proportion of risk factors in our cohort is similar to published literature. As a substantial number of pregnant women do not have identifiable risk factors for development of GDM, our study supports the concept of universal screening of all pregnant women rather than high-risk groups.

In our study, 22 women (44%) were controlled on diet and exercise whereas 28 (56%) women required insulin for maintaining blood sugar levels. According to Sunsaneevithayakul *et al*, 20 out of 33 cases (60.6%) of GDM, whose FBS (from OGTT) was  $\geq 105$  mg/dl could avoid insulin therapy after attending the ambulatory programme alone or with additional 3-day intensive dietary therapy course<sup>15</sup>. In a study done by Kale *et al*, 61% women required insulin and 39% of the women were treated with diet and exercise. Though diet and life style modification are helpful in achieving better glycaemic control, use of insulin therapy should not be unduly delayed as tight glycaemic control is essential for preventing maternal and fetal complications<sup>16</sup>.

Incidence of most complications in our study was quite low and manageable. Kalra *et al* (2013) in a prospective study on prevalence of GDM and its outcomes in Western Rajasthan found the most common complications among the GDM mothers were gestational hypertension (36.4%), vaginal candidiasis (24.2%), premature rupture of membranes (18.1%) and abruptio placentae (12.12%). The prevalence of hypoglycaemia and hyperbilirubinaemia was found to be higher in the GDM group but it was not found to be statistically significant<sup>10</sup>. Landon *et al* (2011) evaluated the relationship between maternal glycaemia and perinatal outcomes in 1,842 women. Analysis of various OGTT categories showed an increasing relationship between fasting and all post-glucose load levels and various perinatal outcomes (neonatal hypoglycaemia, hyperbilirubinaemia, perinatal trauma or death)<sup>17</sup>. Zawaiejska *et al*, in their retrospective observational study using IADPSG criteria, found that maternal fasting hyperglycaemia was associated with significantly higher proportion of macrosomia (19.3% vs 9.7%)<sup>18</sup>. Koshniat *et al* (2010) reported strong association between maternal glucose tolerance and fasting plasma glucose and macrosomia<sup>19</sup>. Incidence of complications varies with the ethnicity, predisposing risk factors and degree of glycaemic control. In our cohort, all the women were booked in the ante-natal clinic, followed up and screened regularly as per guidelines and were, therefore, diagnosed in-time and given appropriate treatment.

Maximum effort was made to control the blood sugar and target levels were achieved in most of the cases. This could be the reason for comparatively lower incidence of complications in our study.

The main limitation of our study is the small sample size and that the events were not compared to pregnant women without GDM.

Our study highlights the importance of dietary counseling, life style modification and appropriate timely institution of pharmacological therapy to reduce the morbidity and mortality associated with GDM. Larger studies are advocated to confirm our findings.

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## Tuberculosis Among Medicine Residents – A Neglected/Alarming Fact

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### Abstract

**Introduction:** Nosocomial transmission of tuberculosis, from patients to healthcare workers, has been known for a long time. India accounts for one fourth of the global tuberculosis burden. With such a high incidence, along with lack of TB control measures in Government-run healthcare facilities, physicians working at these facilities are at constant risk of acquiring infection from patients.

**Material and methods:** The study was conducted in LLRM Medical College, Meerut. All resident doctors who took admission to post-graduate courses after June 2014, were followed-up till June 2016 and those who took admission between June 2011 and June 2014 were interviewed regarding the development of pulmonary or extra-pulmonary tuberculosis. The method adopted was questionnaire based.

**Results:** Out of a total of 325 junior residents, 11 developed tuberculosis during their post-graduate course. Of these, 6 (55%) had pulmonary, and 5 (45%) had extra-pulmonary tuberculosis, with 2 residents from obstetrics and gynecology, 1 from paediatrics, 1 from surgery, and 7 from internal medicine department. 1 resident from internal medicine later developed XDR-TB. There was a total of 765.3 person-years of exposure, with an incidence of 1,437.35 per 1,00,000 person-years of exposure.

**Discussion:** The increased incidence of tuberculosis among internal medicine residents may be due to frequent direct contact with patients in wards whose diagnosis was delayed, poor doctor-patient ratio in internal medicine OPDs, poor personal protection, lack of proper ventilation, long working hours of the residents with negligence towards health and nutrition.

**Conclusion:** There is a high risk of nosocomial transmission of tuberculosis from patients to residents, especially those of internal medicine. Simple measures like proper and early diagnosis, isolation of patients, adequate ventilation, and personal protection could decrease such transmission.

**Key words:** Tuberculosis, nosocomial transmission, MDR, XDR, ventilation, aerosols.

### Introduction

Nosocomial transmission of tuberculosis from patients to healthcare workers has been known since the 1950s<sup>1,2</sup>. This led to the formulation of various guidelines for prevention of transmission of infection of *Mycobacterium tuberculosis* in healthcare settings<sup>3,4</sup>. While the effective implementation of these guidelines has led to a much reduced risk of acquiring nosocomial tuberculosis in HCWs of high – income countries<sup>4</sup>, the situation in low- and middle-income countries, including India, is quite the opposite, with limitation of resources, lack of proper utilisation of resources and lack of awareness among healthcare workers<sup>5</sup>.

India accounts for one fourth of the global tuberculosis burden, i.e., 2.2 million of the incident worldwide annual cases in 2015. In India, everyday > 6,000 people develop tuberculosis and > 600 people die of tuberculosis (2 deaths every 5 minutes). Also, there were 71,000 reported cases of MDR-TB in 2015 from India, and 2,130 of 7,234 patients of XDR-TB in the world were from India<sup>6,7</sup>. With such high incidence, along with lack of TB control measures in

Government-run healthcare facilities, the physicians working in close contact with patients of tuberculosis, at these facilities, are at a constant risk of acquiring the infection.

There are a number of factors responsible for increased risk of transmission of infection in the healthcare settings. These include undue delay in diagnosis and treatment of inpatients, lack of proper isolation of sputum positive cases, lack of timely recognition of drug resistance in patients, overcrowding and poor ventilation in out-patient departments with increased exposure during the undiagnosed state<sup>8</sup>, exposure to aerosols during performance of invasive procedures<sup>9</sup>, lack of or inadequate usage of personal protection measures, and above all, lack of resources, apathy from the administration and lack of knowledge with perceived lack of vulnerability are some of the important risk factors<sup>10</sup>.

Also, the risk of infection becomes higher with increased direct contact with patients, as is seen with physicians, nursing staff, technicians and respiratory therapists<sup>8</sup>.

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This matter has become especially important in view of the increased incidence of drug-resistant tuberculosis, which may be life-threatening, once acquired.

## Materials and methods

The study was conducted in LLRM Medical College, Meerut. All the resident doctors who took admission in the different clinical and non-clinical branches of the institute after June 2014, were followed-up till June 2016. Also all resident doctors who took admission at the institute between June 2011 and June 2014 were queried regarding the development of any type of pulmonary or extra-pulmonary tuberculosis during their duration of the course in the college. The method adopted was questionnaire method. All residents who had pulmonary or extra-pulmonary tuberculosis, as diagnosed by radiology, histology, smear or culture of sputum, body fluids or biopsy specimens positive for mycobacteria, or improvement of signs and symptoms with anti-tuberculosis treatment were included.

## Results

Out of a total of 325 junior residents who took admission in the various departments of the college between June 2011 and June 2016, 11 residents developed tuberculosis during their course.

Of these, 6 (55%) had pulmonary, and 5 (45%) had extra-pulmonary tuberculosis (2 of pleural – effusion, and, 1 each of Pott’s spine, Genito-urinary tuberculosis, and tubercular choroiditis). There were 7 male and 4 female residents,

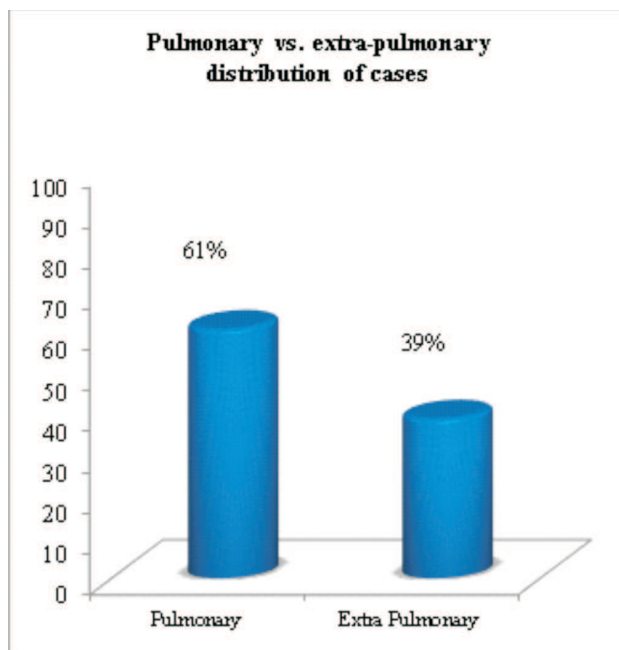


Fig. 1:

who developed tuberculosis.

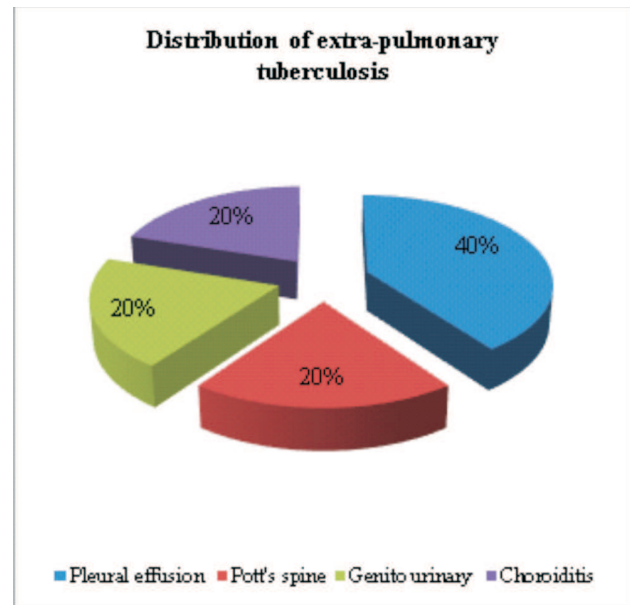


Fig. 2:

All the 11 residents belonged to the clinical branches, out of which 2 residents were from obstetrics and gynecology, 1 from paediatrics, 1 from surgery, and 7 from Internal Medicine department. All the residents belonged to the age-group of 25 - 35 years.

Batch	Internal medicine	Obstetrics and gynaecology	Paediatrics	General surgery
2011 - 12	2	0	0	0
2012 - 13	3	0	0	0
2013 - 14	1	1	0	0
2014 - 15	1	1	0	0
2015 - 16	0	0	1	1

During the study period 1 resident from internal medicine suffered from MDR-tuberculosis, and later developed XDR-TB. He could not complete his training due to ill health, and is still fighting for life.

There was a total of 765.3 person-years of exposure, with an incidence of 1,437.35 per 1,00,000 person-years of exposure.

## Discussion

It was observed that out of the 11 residents who developed tuberculosis during their course-duration, the majority of residents, i.e., 7 out of 11 (64%) belonged to the department of internal medicine, 4 of whom developed extra-pulmonary tuberculosis and 3 developed pulmonary tuberculosis (1 developed XDR-tuberculosis later on). The increased incidence of tuberculosis in internal medicine

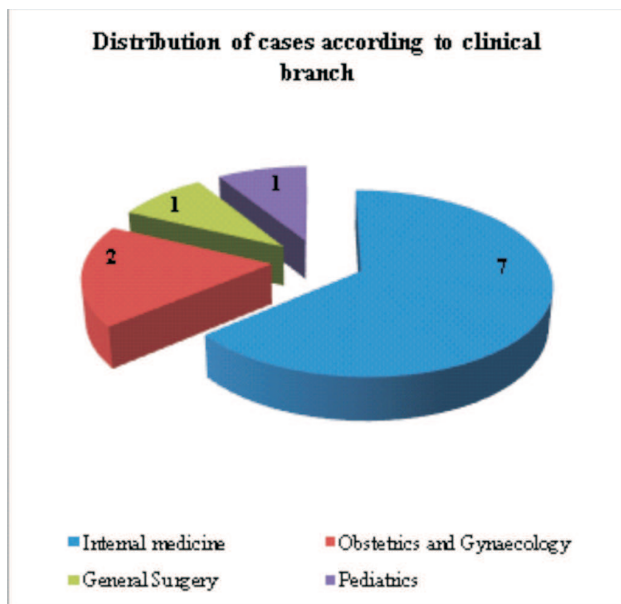


Fig. 3:

residents may be attributable to a number of factors, like, frequent direct contact with patients in wards<sup>8</sup>, increased exposure to infectious aerosols while doing diagnostic and therapeutic procedures<sup>9</sup>, increased likelihood of infection from patients with delayed diagnosis (as patients usually approach internal medicine doctors first with their symptoms), poor doctor-patient ratio in internal medicine OPDs (with an average of > 100 patients per doctor on any average day)<sup>10</sup>. Poor personal protection, lack of proper ventilation while working with sputum-positive cases are important risk factors too. Long working hours of the residents with negligence towards health and nutrition also appear to be contributory factors. Moreover, with the epidemic of HIV in Western UP, increased exposure to patients with HIV plus TB is also a risk factor for increased incidence of tuberculosis.

## Conclusion

There is a high risk of nosocomial transmission of tuberculosis from patients to resident doctors working in close contact with them, especially those of internal medicine. This requires urgent steps to be taken at the administrative and personal level to stop tuberculosis from becoming an occupational hazard in the field of medicine. Simple measures like proper and early diagnosis, isolation of patients during the period of infectivity, adequate ventilation, and personal protection by means of respiratory masks could go a long way in doing the same.

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**The name of the corresponding author with his/her affiliation, address, telephone number, and E-mail ID must be indicated separately in the title page of the submitted manuscript.**

## Association of 25-Hydroxy Vitamin D, Endothelial Dysfunction and Coronary Artery Disease in Angiographically Studied Cases

SH Talib\*, MR Naik\*\*, Vikrant Patil\*\*\*, Vinay Joshi\*\*\*\*, Shivam Dutt\*\*\*\*\*

### Abstract

*The quest to identify new predictors of cardiovascular disease has focused the attention on vitamin D, given its association with endothelial dysfunction and established risk factors for coronary artery disease. This underlines the importance of clarifying the role of vitamin D in the context of cardiovascular disease in the Indian population.*

*Aim: To find the association between levels of vitamin D, endothelial dysfunction and coronary artery disease among subjects undergoing coronary angiography.*

*Methods: 117 cases, undergoing coronary angiography, were included. Vitamin D status and flow mediated dilation of brachial artery were assessed to look for their correlation with extent of vessel involvement in coronary artery disease. Various risk factors and biochemical markers were also assessed to look for correlation with vitamin D status.*

*Results: The mean value of [25-hydroxyvitamin D 25 (OH) D] was  $16.29 \pm 8.70$  ng/ml. Patients with vitamin D deficiency had higher frequency of single/double/triple-vessel disease (78.6%, 84.6% and 78.9%, respectively) as compared to those having insufficiency and sufficiency. The mean brachial artery flow mediated vasodilatation of the studied cases was  $7.44 \pm 2.94$ . There was significant association between endothelial dysfunction and coronary artery disease ( $p < 0.0001$ ). The relationship of 25 (OH) D levels and endothelial dysfunction was recognised, with inverse proportions.*

*Conclusion: Vitamin D deficiency and endothelial dysfunction were independent risk factors for coronary artery disease. Vitamin D deficiency was predominantly observed in patients with moderate to severe coronary artery disease. Endothelial dysfunction was significantly correlated with extent of vessel involvement and vitamin D insufficiency and/or deficiency.*

*Key words: Vitamin D deficiency, endothelial dysfunction, flow mediated dilation of brachial artery, coronary artery disease.*

### Introduction

Vitamin D has been traditionally associated with bone health but adequate levels are also important for optimal cardiovascular (CV) function. The discovery that vitamin D receptors are ubiquitously expressed in almost all body cells, such as immune, vascular or myocardial cells, suggests an involvement of vitamin D-mediated effects in several other systems, apart from musculoskeletal tissues<sup>1</sup>. Vitamin D deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world<sup>2</sup>. This has led to extensive research on vitamin D as a potential influencing factor in the pathogenesis of several chronic non-skeletal diseases, such as infections, autoimmune diseases, cancer and cardiovascular diseases (CVD)<sup>3</sup>.

Vitamin D also has associations with various established risk factors for CVD, like hypertension, diabetes, obesity, metabolic syndrome, congestive heart failure, and coronary artery disease<sup>4</sup>. Vitamin D deficiency has also been linked to an increased risk of myocardial infarction, cardiovascular death, and overall mortality<sup>5</sup>. However, other studies have

reported an absence of significant correlation of vitamin D with cardiovascular diseases, necessitating further studies to prove a potential link between the two<sup>6</sup>. Despite abundant sunshine, vitamin D deficiency is frequent among Indians<sup>7</sup>. This is due to lack of vitamin D supplementation in diet, malnutrition and high degree of coverage of the body with clothing, thus precluding adequate synthesis of the vitamin. Moreover, a darker skin pigmentation, as noted with Asians, requires greater degree of exposure to the sun to be able to synthesize equivalent amounts of vitamin D, compared to people with lighter skin colour<sup>8</sup>.

On the other hand, endothelial dysfunction is an important antecedent event in the development of atherosclerosis and CVD<sup>9</sup>. Vitamin D is known to affect vascular endothelium through up-regulation of the renin-angiotensin system or via induction of a pro-inflammatory state and smooth muscle proliferation<sup>10</sup>. It is, therefore, important to study the relationship between vitamin D deficiency and endothelial dysfunction, assessed by brachial artery flow mediated dilatation (FMD).

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Despite the rising prevalence of coronary artery disease (CAD) in Indians, studies of vitamin D levels and endothelial dysfunction in patients with angiographically documented CAD population, are limited and conflicting<sup>11</sup>.

**Aim:** To search for and analyse any association between levels of vitamin D, endothelial dysfunction and CAD among subjects undergoing coronary angiography at this centre.

**Objectives:** (a) To analyse levels of (25 OH D) in subjects of coronary artery disease, undergoing coronary angiography (CAG), (b) analysis of these cases for scores of FMD to study endothelial function, (c) to correlate the data of FMD score and 25 (OH) D levels with coronary angiography findings, (d) to know the frequency of single vessel disease (SVD), double vessel disease (DVD), triple vessel disease (TVD) in association with 25 (OH) D levels and its correlation with endothelial dysfunction, and (e) to analyse the significance of 25 (OH) D levels in patients with various metabolic and biochemical parameters like fasting and post-prandial plasma glucose, glycosylated haemoglobin, lipid profile, renal function tests, serum calcium and phosphorus levels.

## Material and methods

### Research study design

Study design: Cross-sectional, observational study.

Study setting: MGM Medical College and Hospital, Aurangabad.

Study duration: Nov 2015 - Nov 2017.

Sampling technique: Random sampling.

Sample size: 117.

The study was approved by the ethics committee of MGM University. Written and informed consents for the present study were taken from all subjects.

**Exclusion criteria:** Cases on therapy with vitamin D supplements for at least two months, persons with history of primary cardiac diseases, rheumatic diseases, intestinal disorders, thyroid disorders, parenchymal liver diseases, kidney diseases and sepsis. Patients who were critically ill and could not undergo FMD testing were excluded.

Anthropometric features including weight, height, and body mass index, were measured by standard methods. Blood pressure was measured with a standard mercury sphygmomanometer in supine position in right arm with a standard size cuff, after one minute rest. Mean values were determined from two independent measurements taken at a 5 minute interval. The patient was labelled hypertensive, if the systolic blood pressure was more than 140 mm Hg or diastolic blood pressure was more than 90 mm Hg.

Besides, clinical examination, biochemistry measurements including fasting and post-prandial blood sugar, oral glucose tolerance test, serum total cholesterol, triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were done after keeping the patient fasting for 10 - 12 hours. Other haematological investigations like renal function tests, serum calcium and phosphorus levels were also performed.

**Estimation of serum vitamin D:** For 25(OH) D, a 3 ml venous, blood sample was collected from the participant at 8 am in the morning and taken to laboratory and processed on the same day. The method of estimation was cobalt metal immunoassay. The detection limit for 25 (OH) D was 5 ng/ml, with a reported inter-assay variation coefficient of approximately 10%. Low vitamin D was considered as 25 (OH) D levels of less than 30 ng/ml, vitamin D deficiency was defined as 25 (OH) D level of  $\leq 20$  ng/ml, vitamin D insufficiency as levels between 21 to 29 ng/ml, while optimal levels were defined as 25(OH) D  $\geq 30$  ng/ml<sup>12</sup>.

**FMD measurement:** Endothelium-dependent brachial artery FMD was measured following reactive hyperaemia<sup>13,14</sup>. Using ANGIODEFENDER™ instrument, measurements of the brachial artery were taken at rest and again after cuff deflation; completing supra-systolic compression of 30 mmHg above systolic BP for 5 minutes at right upper arm. Scans of brachial artery were taken proximal to the bifurcation of the radial and the ulnar artery by tying the cuff. Measurement of diameters were recorded at baseline and following hyperemia from one media-adventitia interface and mean readings were taken. Maximum flow diameter was measured in all subjects at rest, and within 15 seconds of cuff deflation. Vasodilatation was calculated as the percentage change in diameter compared to baseline. FMD values more than 10% are suggestive of normal vessels, whereas the values between 6 - 10% and lesser than 6% show the impaired endothelial function and established endothelial dysfunction respectively<sup>13,14</sup>.

Diagnosis of pre-diabetes and diabetes was made in accordance with American Diabetes Association criteria (2016)<sup>15</sup>.

Angiographic CAD was defined as stenosis of  $> 50\%$  in any of the major epicardial coronary arteries.

**Statistical analysis:** The collected data was entered in MS Excel sheet. All the analysis was done by using the windows based SPSS statistical package (version 15.0, spssinc: Chicago, IL, USA and p values  $< 0.05$  were taken as the level of significance). The qualitative data was represented in the form of frequencies and percentages. The quantitative data was represented in the form of mean,

standard deviation, and 95% CI. Student's T-test was applied, as appropriate, to compare the means between two groups. The chi-square test or Fisher's exact test was used to find association between two attributes. The Pearson's correlation analysis was done to determine relationship of vitamin D3 levels with FMD. For comparison of Quantitative data with three groups, ANOVA was applied.

## Results

The present study was carried out at a tertiary care hospital, and included 117 participants of which 91 (77.8%) were males and 26 (22.2%) were females. The participants' age in our study ranged from 33 - 75 years. The mean age was  $56.57 \pm 9.93$  years. They were further sub-grouped in five age groups, i.e., 30 - 40, 41 - 50, 51 - 60, 61 - 70, and > 70 years. Most of the patients were from age group 51 - 60 years (35.9%).

CAG findings in our study revealed 11 (9.40%) had normal/insignificant CAD, 42 (35.89%) had SVD, while DVD and TVD was found in 26 (22.22%) and 38 (32.48%) participants, respectively. The mean vitamin D level in all studied cases was  $16.29 \pm 8.70$  ng/ml, which was lower than normal limits (Table I). Vitamin D status of 13 (11.1%) participants showed sufficiency (levels  $\geq 30$  ng/ml), 12 (10.3%) had insufficiency (21 - 29 ng/ml) while 92 (78.6%) had deficiency ( $\leq 20$  ng/ml). We observed no significant variation of vitamin D levels in different age groups (p value = 0.699). Comparison of vitamin D status with demographic characteristics like gender and BMI, was found statistically insignificant (p values of 0.887, 0.256 respectively).

We observed a higher rate of hypovitaminosis D (insufficiency and deficiency) in studied patients with angiographically documented CAD (82.9%). Patients with lower levels ( $\leq 20$  ng/ml) of vitamin D had higher prevalence of CAD (SVD - 78.6%, DVD - 84.6% and TVD - 78.9%), on CAG. We observed that prevalence of vitamin D deficiency was very high in patients with CAD but vitamin D deficiency and the severity of deficiency did not correlate with angiographic severity of CAD (p value

= 0.814)(Table II). Vitamin D deficiency was also highly prevalent (45.45%) in patients with angiographically proven normal coronary artery and/or insignificant CAD (< 50% occlusion on CAG) who presented with symptoms of angina and had ECG changes.

Comparison of different levels of vitamin D and its effect on various biochemical markers such as total cholesterol, TG, LDL and HDL showed no significant correlation (P = 0.383, 0.067, 0.477 and 0.352, respectively). No significant correlation was observed with fasting or post-prandial sugar and HbA1c levels (P = 0.268, 0.244, 0.301, respectively). Serum calcium levels were found to be lower in participants having lower vitamin D levels, but no significant correlation was observed with serum calcium and phosphorus levels (P = 0.390 and 0.754, respectively)(Table III).

We found vitamin D insufficiency and/or deficiency in 17 (14.52%) pre-diabetic patients, 27 (23.07%) diabetic patients, 46 (38.31%) patients with hypertension and 34 (29.05%) patients who were smokers. There was no significant correlation between vitamin D status and the above risk factors in the present study (p value = 0.996, 0.251, 0.469 and 0.196, respectively). This observation could be attributed to low levels of vitamin D in the general Indian population. Patients presenting with either acute coronary syndrome or chronic stable angina had insignificant correlation with vitamin D status (P = 0.054, 0.054, respectively) (Table III).

**Table I: Distribution of patients according to 25 (OH) D status.**

25 (OH)D status	Male		Female		Total	
	No.	%	No.	%	No.	%
Sufficient ( $\geq 30$ ng/ml)	10	11.0%	03	11.5%	13	11.1%
Insufficiency (21 - 29 ng/ml)	10	11.0%	02	7.7%	12	10.3%
Deficient ( $\geq 20$ ng/ml)	71	78.0%	21	80.8%	92	78.6%
Total	91	100%	26	100%	117	100%
Mean $\pm$ SD	$16.19 \pm 8.81$		$16.63 \pm 8.48$		$16.29 \pm 8.70$	

**Table II: Association between 25 (OH) D levels and extent of vessel involvement in CAG.**

25 (OH) D status	Insignificant CAD		SVD		DVD		TVD		Chi-square value	P - value
	No.	%	No.	%	No.	%	No.	%		
Sufficient ( $\geq 30$ ng/ml)	04	36.37%	05	11.9%	01	3.8%	03	7.9%	1.57	P = 0.814
Insufficiency (21 - 29 ng/ml)	02	18.19%	04	9.5%	03	11.5%	05	13.2%		
Deficient ( $\leq 20$ ng/ml)	05	45.46%	33	78.6%	22	84.6%	30	78.9%		
Total	11	100%	42	100%	26	100%	38	100%		

**Table III: Comparison of different biological markers and risk factors with 25 (OH) D status.**

	Sufficient ( $\geq 30$ ng/ml) (N = 13)	Insufficiency (21 - 29 ng/ml) (N = 12)	Deficient ( $\leq 20$ ng/ml) (N = 92)	F-value/Chi-square value	p-value
Total cholesterol (mg/dl)	162.46 $\pm$ 34.31	181.41 $\pm$ 32.91	172.53 $\pm$ 34.28	0.969	P = 0.383
TG (mg/dl)	101.15 $\pm$ 25.68	144.36 $\pm$ 58.09	126.53 $\pm$ 43.34	2.23	P = 0.067
LDL (mg/dl)	83.83 $\pm$ 21.88	84.24 $\pm$ 29.29	92.31 $\pm$ 31.12	0.747	P = 0.477
HDL (mg/dl)	37.77 $\pm$ 7.59	34.00 $\pm$ 6.70	36.68 $\pm$ 6.77	1.05	P = 0.352
Blood glucose (F) (mg/dl)	97.15 $\pm$ 21.44	110.17 $\pm$ 46.02	115.20 $\pm$ 38.30	1.33	P = 0.268
Blood glucose (PP) (mg/dl)	141.23 $\pm$ 27.95	161.50 $\pm$ 88.32	177.72 $\pm$ 79.04	1.43	P = 0.244
HbA1c (%)	5.40 $\pm$ 0.61	5.85 $\pm$ 1.67	6.03 $\pm$ 1.41	1.21	P = 0.301
Sr. calcium (mg/dl)	8.01 $\pm$ 0.68	8.08 $\pm$ 0.73	7.83 $\pm$ 0.67	0.949	P = 0.390
Sr. phosphorus (mg/dl)	4.08 $\pm$ 0.62	4.40 $\pm$ 1.25	4.20 $\pm$ 1.08	0.283	P = 0.754
Pre-diabetic Yes/No	02/11	02/10	15/77	0.009	P = 0.996
Diabetes Yes/No	01/12	02/10	25/67	2.76	P = 0.251
Hypertension Yes/No	04/09	04/08	42/50	1.51	P = 0.469
Smoking Yes/No	02/11	02/10	32/60	3.26	P = 0.196
ACS Yes/No	07/06	05/07	66/26	5.40	P = 0.054
CSA Yes/No	06/07	07/05	26/66	5.40	P = 0.054

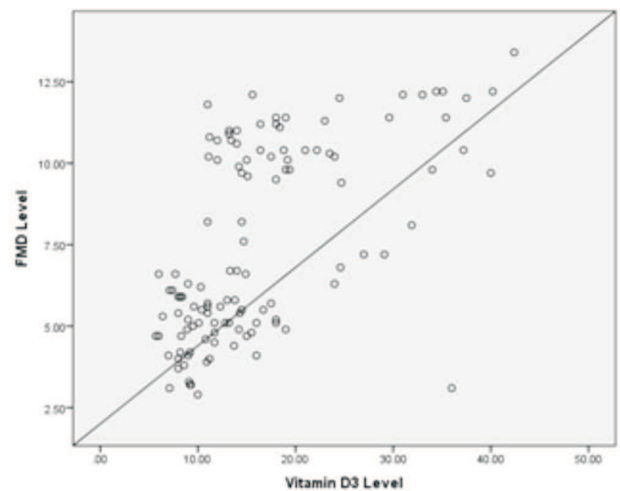
The mean FMD measured in the 117 studied cases was  $7.44 \pm 2.94$ . Normal FMD score ( $> 10\%$ ) was found in 37 (31.62%), impaired FMD score (6 - 10%) was present in 25 (21.36%), and established endothelial dysfunction ( $< 6\%$ ) was found in 55 participants (47%).

Low mean FMD score ( $6.75 \pm 2.67$ ) was observed more commonly among patients having vitamin D deficiency than among those who had normal ( $10.67 \pm 2.68$ ) or insufficient ( $9.41 \pm 1.99$ ) FMD score. Low vitamin D status was considered as independent contributing risk factor for endothelial dysfunction (r value = 0.593, p value =  $< 0.0001$ ) (Table IV). Linear graph of comparison of the FMD score with vitamin D levels was suggestive of the significant association (Fig. 1).

**Table IV: Comparison of mean FMD score with 25 (OH) D status.**

25 (OH) D status	Mean FMD score	F-value	P-value
Sufficient ( $\geq 30$ ng/ml)	10.67 $\pm$ 2.68	16.39	P = $< 0.0001$
Insufficiency (21 - 29 ng/ml)	9.41 $\pm$ 1.99		
Deficient ( $\leq 20$ ng/ml)	6.75 $\pm$ 2.67		
Total	7.44 $\pm$ 2.94		

The extent of the involvement of vessels, as assessed on CAG increased with decreasing FMD Score. Most patients having SVD had normal endothelial function (45.2%), those

**Fig. 1:** Linear graph showing correlation of FMD score with vitamin D levels.

with DVD had either impaired function or established endothelial dysfunction (38.5% each) and those with TVD had 81.6% endothelial dysfunction. Endothelial dysfunction as assessed by FMD was more frequently observed in those with DVD (38.5%) and TVD (81.6%), when compared with SVD (26.19%) and non-significant CAD (18.18%). A significant association was recorded between endothelial dysfunction and coronary artery disease, irrespective of degree of vessel involvement (P =  $< 0.0001$ ) (Table V).

**Table V: Association between endothelial function (FMD score) and extent of CAD.**

Endothelial function	SVD		DVD		TVD		Chi-square value	P-value
	No.	%	No.	%	No.	%		
Normal (>10%)	19	45.2%	06	23.1%	04	10.5%	29.1	P = < 0.0001
Impaired (6 - 10%)	12	28.6%	10	38.5%	03	7.9%		
Dysfunction (<6%)	11	26.19%	10	38.5%	31	81.6%		
Total	42	100%	26	100%	38	100%		

## Discussion

In the present study among 117 cases, vitamin D deficiency was observed in 78.6%, insufficiency in 10.3%, while 11.1% had optimal levels. This high prevalence of the vitamin D deficiency, could reflect the baseline high prevalence of hypovitaminosis D in Indian population. The high prevalence rates in our country, despite the sunny climate and proximity to the equator, are explained by the darker skin complexion of the population, generalised malnutrition, inadequate sun exposure, vegetarian food habits and lack of vitamin D food fortification programme<sup>16</sup>.

In our study, though there was a mixed trend towards lower mean 25 (OH) D levels with increasing severity of CAD, patients with vitamin D deficiency had higher frequency of SVD, DVD or TVD (78.6%, 84.6% and 78.9% respectively). Patients with triple-vessel disease on coronary angiography had a high prevalence of vitamin D deficiency (89%); similarly, those with diffuse angiographic CAD also had a high prevalence of vitamin D deficiency (84%). This simply suggests that vessel involvement is higher among vitamin D deficient subjects; however, there was no statistical significance in this comparison and it may be a reflection of the high prevalence of vitamin D deficiency in Indians.

The role of vitamin D deficiency in causation of CAD along with various parameters like lipid profile, fasting-post-prandial sugars, HbA1c, serum calcium and phosphorus levels was found to be insignificant, though the values of these parameters were low. Among patients having angiographic CAD the prevalence of risk factors including pre-diabetes (16.23%), diabetes (23.93%), hypertension (42.43%) and smoking (30.76%) was not significantly different in patients, with or without vitamin D deficiency. Though we did not find any significant correlation of vitamin D levels with above parameters and risk factors, an association between vitamin D levels and angiographic

extent of CAD was demonstrable.

Though vitamin D deficiency has previously been shown to be associated with established CV risk factors, higher cardiovascular death, and overall mortality, studies have been heterogenous, and only small numbers of longitudinal studies are available. Recent meta-analyses have been conflicting, as they reported both positive and neutral associations<sup>17</sup>. Moreover, data on the spectrum and severity of vitamin D deficiency and extent of angiographically determined CAD are limited. Possibly, studies with larger numbers of patients, with multiple centres involved, would be able to demonstrate more robust and statistically significant associations.

The observations of past meta-analyses are misleading as they could be influenced by confounding factors, such as increased age, obesity and serum levels of PTH, renin, calcium, phosphorus. The reduced mobility and physical activity in chronically ill patients, leading to reduced sunlight exposure and lower vitamin D levels, is also an important confounding factor<sup>18</sup>. In our study, we could rule-out confounders like gender, age, obesity, deranged lipid profile, fasting and post-prandial sugars, serum calcium and phosphorus levels. The correlation of various confounders with vitamin D levels was found to be insignificant in our study (Table III).

Studies on correlation of 25 (OH) D levels and angiographically documented CAD, have reported conflicting results in Indian literature. Though Shanker *et al*, in 2011, found that low vitamin D levels were associated with increased risk for CAD and patients in the lower vitamin D quartile had significantly higher risk for CAD, an association with severity of CAD was reported insignificant<sup>7</sup>. Rajasree *et al*, (2001) reported paradoxical, increased odds of ischaemic heart disease among patients with higher values of 25 (OH) D levels (> 89 ng/ml), compared to those having lower vitamin D levels. This observation is attributed to high intake of regional foods rich in vitamin D, accounting for the deleterious effects<sup>8</sup>. The subject is still open and the findings of ongoing randomised controlled trials would provide all the final answers to the question whether this vitamin proves useful for the prevention and treatment of CVD<sup>19,20</sup>. Although therapeutic aspects of supplementation of vitamin D and its preventive consideration was not the objective of our study; a study on usefulness of vitamin D in preventing cardiovascular disease and hypovitaminosis D is; however, warranted. Since the majority of studied cases and the present study have shown significantly higher percentage of individuals developing atherogenicity and CAD, an early detection of endothelial dysfunction with FMD and



vitamin D status is desirable, especially in young Indians.

We observed that mean FMD values were markedly reduced in patients with vitamin D deficiency. A graded relationship between 25 (OH) D levels and FMD was observed in our study (Table IV). The FMD score and extent of CAD, an CAG, showed a directly proportional relationship. Among patients with SVD, DVD and TVD, 54.8%, 78% and 81.6%, respectively had endothelial dysfunction assessed by FVD (Table V).

Effect of vitamin D on endothelial function is postulated to be either direct via modulation of calcium influx or by indirect mechanisms, including protection against oxidative stress and lipid peroxidation<sup>21</sup>. It has also been shown that vitamin D supplementation in deficient individuals is associated with improvements in parameters of vascular function, thus further strengthening its association with impaired FMD<sup>22</sup>.

In routine clinical settings, risk for atherosclerotic cardiovascular disease is estimated by identifying and quantifying the traditional risk factors, yet no consideration is given to non-traditional risk factors like assessment of endothelial dysfunction and vitamin D status. Thus, in addition, traditional assessment measures the FMD score and vitamin D status, especially, in young could prove beneficial for detecting the future risk of atherogenicity.

## Conclusion

Vitamin D deficiency and endothelial dysfunction are independent risk factors for coronary artery disease. Low vitamin D levels may be an independent and potentially modifiable cardiovascular risk factor, but whether vitamin D supplementation can significantly improve cardiovascular outcomes is still unknown; as we did not need to this objective in our study and also the literature lacks robust evidence. The correlation of vitamin D deficiency with the extent of vessel involvement in coronary artery disease was noted insignificant. However, on the contrary, patients with double- and triple-vessel disease had higher percentage of vitamin D deficiency. Endothelial dysfunction, measured by flow mediated dilation of brachial artery, was associated more often with double- and triple-vessel disease and with vitamin D insufficiency and/or deficiency. Recognition of endothelial dysfunction could help in preventing cardiovascular events in future, if the application of the FMD score/vitamin D status is considered as a vital measure.

## Limitation

Further studies with large sample size from multiple

centres, may be useful in reducing the conflicts in correlation of hypovitaminosis D and status of coronary heart disease.

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# To Study the Association of Lipid Pentad Index with Coronary Artery Disease in Diabetic Patients and its Comparison with Lipid Tetrad Index

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## Abstract

Despite of a paucity of traditional risk factors, in our country prevalence of Coronary artery disease (CAD) is quite high. It has a more malignant course than in the west. To explain this phenomenon, various non conventional risk factors and indices have been proposed. Two important indices are – Lipid tetrad index and lipid pentad index. In India, diabetes is also an important contributing factor in the epidemic of CAD. The present study was undertaken to compare these two indices to explain the magnitude of CAD in Indian diabetic patients. Out of these, lipid pentad index has probably more sensitivity and specificity (sensitivity - 100%, specificity - 97.5%) as compared to that of lipid tetrad index (sensitivity - 98.3%, specificity - 95%).

**Key words:** Lipid tetrad index, lipid pentad index, non conventional risk factors, CAD.

## Introduction

Despite of a paucity of traditional risk factors in CAD in Indian patients, the prevalence of CAD is high and pattern of CAD is also different. In India, the course of CAD is more malignant and patients affected are younger.

With the global epidemic of diabetes, India is also facing the challenge of diabetes and will soon become the diabetes capital the world. The present prevalence of diabetes in India is 62 million adults<sup>1</sup>. To assess the risk factors in Indian pattern of CAD, Enas *et al* first described a lipid tetrad index (LTI) which is multiplication of total cholesterol, triglyceride and lipoprotein (a) and division of this product by HDL<sup>2</sup>. Subsequently, another index was described by Das *et al*, known as lipid pentad index, to assess the burden of CAD in Indian patients<sup>3</sup>. Lipid Pentad Index (LPI) comprises the product of four atherogenic particles namely total cholesterol, triglyceride, lipoprotein (a) and apolipoprotein B divided by apolipoprotein A1<sup>3</sup>. Lipid pentad index (LPI) and Lipid tetrad index (LTI) have been studied in various groups throughout the country, however no study has compared them in diabetic patients. Therefore, this study was conducted to find out the best single index for predicting the risk of CAD among Indian diabetic patients.

## Material and methods

The study was a hospital based case-control study. It was done among diabetic patients visiting the outpatient department and diabetes clinic of PG Department of

Medicine and Cardiology Department of SN Medical College, Agra from June 2014 to May, 2016. 120 diabetic patients, with or without CAD, were taken and divided into two groups A and B each and LPI and LTI were calculated in both groups as mentioned above and analysed using appropriate statistical methods. Group A included diabetic patients with CAD who were hs troponin T +ve, with ECG changes and history of chest pain and without any other significant risk factors (obesity, smoking, alcohol, hypertension). Patients in group B were type 2 diabetics without any history of CAD. Pregnant women, patients with any chronic disease like TB, hypertension, diabetic patients on lipid lowering drugs, those diagnosed within last 5 years and those not willing to give consent were excluded from the study.

All patients gave informed consent, and underwent thorough history, clinical examination and relevant investigations including serum total cholesterol, triglyceride, HDL cholesterol, lipoprotein (a), apolipoprotein A1 and apolipoprotein B. For each subject, information was obtained by a directly administered questionnaire. This was recorded in a predesigned proforma. Total cholesterol, triglyceride and HDL cholesterol were estimated using enzymatic – colorimetric method and lp(a), Apo A1 and Apo-B were estimated by immunoturbidimetry. LTI and LPI were calculated using the above mentioned method [Lipid Tetrad index = Total cholesterol x triglyceride x lipoprotein (a)/HDL; Lipid pentad index = Total cholesterol x triglyceride x lipoprotein (a) x apolipoprotein B/apolipoprotein A1].

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## Results

There were 60 patients in the case group and 60 patients in the control group. In the case group, 39 patients were male, and 21 patients were females. In the control group, 37 patients were males and 23 patients were female. The mean age of patients in the case group was  $50.23 \pm 8.26$  and in control group was  $46.65 \pm 8.75$  years. hs trop T levels, signifying coronary artery disease, were significantly higher in case group ( $323.84 \pm 309.77$  vs  $9.74 \pm 2.97$ ;  $p < 0.0001$ ). Serum total cholesterol (TC), triglyceride (TG), lipoprotein(a) and apolipoprotein B were significantly higher in the case group as compared to control group as shown in Table I. Serum HDL and apolipoprotein A1 levels were significantly lower in case group (Table I).

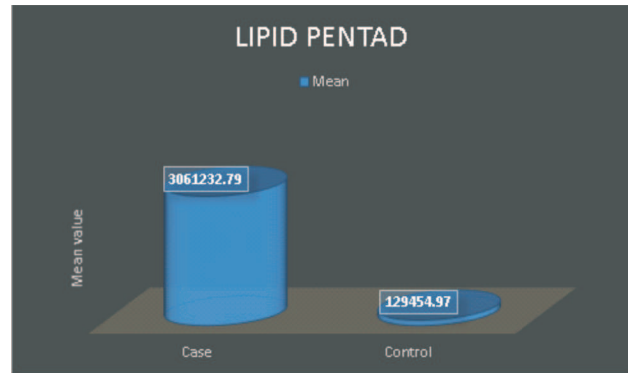


Fig. 1: Lipid Pentad index values in cases and controls.

Table I: Showing various lipid and apolipoprotein variables in case and control group.

	Total cholesterol (TC) mg/dl	Serum triglyceride (TG) mg/dl	Lipoprotein (a) (LPa) mg/dl	Apolipoprotein B (Apo B) mg/dl	Apolipoprotein A1 (ApoA1) mg/dl	HDL mg/dl
Group A (cases)	$287.86 \pm 53.49$	$292.99 \pm 62.84$	$37.32 \pm 10.25$	$242 \pm 46$	$152 \pm 35$	$37.27 \pm 4.53$
Group B (control)	$104.61 \pm 42.16$	$162.28 \pm 21.99$	$12.88 \pm 5.38$	$86 \pm 19$	$260 \pm 31$	$51.88 \pm 10.78$
p value	$< 0.0001$	$< 0.0001$	$< 0.0001$	$< 0.0001$	$< 0.0001$	$< 0.0001$

Table II: Lipid tetrad index values in case and control group.

Lipid tetrad index	Case		Mean $\pm$ SD	Control		Mean $\pm$ SD	p-value
	No	%		No	%		
< (20,000)	3	5	$20280.75 \pm 1403.69$	59	98.33	$4459.69 \pm 3328.18$	$< 0.0001$
> (20,000)	57	95.00	$100575.23 \pm 31531.60$	1	1.67	22101.98	$< 0.0001$
	60	100.00		60	100.00		

Using these parameters LTI and LPI were calculated. Both LTI and LPI were significantly higher in case group, as compared to control group (Table II, III and Fig. 1). Only 3 subjects of the case group had LTI values  $< 20,000$  and remaining had values  $> 20,000$  while only one of the control group had values  $> 20,000$  (Table II). Using these values, sensitivity and specificity of LTI was found to be 98.33% and 95%, respectively.

Table III: Lipid Pentad index values in case and control group.

Groups	Lipid pentad index
Group A (case)	$3061232.79 \pm 1448110.55$
Group B (control)	$129454.97 \pm 88738.97$
p value	$< 0.0001$

Using the ROC (receiver operating characteristic) curve in our set of data, the cut-off value of LPI came out to be  $> 351628.2$ . Using this value, the calculated sensitivity of the

LPI was 100% and specificity of the LPI was 97.50%, which is well above those observed for LTI (sensitivity - 98.3%, specificity - 95%).

To assess the association between the various lipid indices, correlation tests were performed between LTI and LPI among cases and controls. The correlation between LTI and LPI was positive among both cases and controls (correlation co-efficient 0.67, in cases and 0.80 in controls).

## Discussion

Compared with nondiabetics, patients with diabetes have a two- to four-fold increased risk of death from CAD. Dyslipidaemia is a very important risk factor in the pathogenesis of CAD, in diabetics. Abnormal lipid parameters have been used for many years as risk factors for CAD. Many studies have proven the importance of conventional lipid parameters, i.e., TC, LDL, HDL, and TG in the pathogenesis of atherosclerosis which is a basic pathology in CAD. But in many cases, the conventional

parameters fail to explain the higher occurrence or severity of CAD in Indian population, which emphasizes that other lipid parameters may be involved in the pathogenesis of CAD.

Lp(a) is categorised as an emerging lipid risk factor by Adult Treatment Panel III of National Cholesterol Education Programme. Elevated Lp(a) level, increases the individual risk to a higher level. High levels of Lp(a) correlate with prematurity, severity, extent, and progression of coronary atherosclerosis as well as occurrence and recurrence of myocardial infarction among Asian Indians. The risk for CAD increases 3-fold in the absence of other risk factors, increases 8-fold with low HDL, 12-fold with high LDL, 16-fold with diabetes, 25-fold with high TC/HDL ratio when associated with increase in plasma Lp(a) levels<sup>4</sup>. The coronary artery disease in Indians (CADI) study<sup>5</sup> first reported the existence of high levels of Lp(a) in Asian Indians as compared to Americans. In Indian population, Enas *et al* suggested Lp(a) of 20 mg/dl as the upper limit of normal. For risk categorisation, Lp(a) levels are desirable < 14 mg/dl, borderline risk – 14 - 30 mg/dl, high risk 31 - 50 mg/dl, and very high risk > 50 mg/dl<sup>6,7</sup>. Mean Lp(a) levels in our study were significantly higher in case group (37.32 ± 10.25) mg/dl when compared with the control group (12.88 ± 5.38) mg/dl. Higher mean plasma Lp(a) levels in the study group correlated with mean Lp(a) levels in CAD group, as also observed by Rajasekhar *et al*<sup>8</sup>, and Isser *et al*<sup>9</sup>.

The comprehensive LTI as proposed by Enas *et al*, is designed to magnify the subtle abnormalities of various atherogenic and antiatherogenic lipoproteins, and described it as a single predictor for CAD risks in diverse populations, especially Asian Indians<sup>10</sup>. When measurements are made in mg/dl, an index of 20,000 is high. An index of more than 1,00,000 is usually associated with marked prematurity and severity of CAD, poor outcome of re-vascularisation including recurrence of restenosis after angioplasty and rapid thrombosis of the coronary stent<sup>11</sup>. In our study, the mean LTI of patients was significantly higher in the case group (100575.23 ± 31531.60) when compared with the control group (22101.98), as has been reported earlier in the studies done by Enas *et al*. Likewise, a review done by Yeolekar *et al*<sup>12</sup> showed that Asians had a deadly LTI which becomes the single most important predictor of CAD in Asian region. LTI calculated in our study showed a specificity of 95.00% and sensitivity of 98.33%.

The ratio of Apo B to Apo A1 reflects the balance of cholesterol transport in a simple way. The higher the value of the Apo B /Apo A1 ratio, the more cholesterol is circulating in the plasma compartment and this cholesterol is likely to be deposited in the arterial wall, provoking atherogenesis and risk of CAD events<sup>13,14</sup>. The lower the

Apo B/Apo A1 ratio, the lower is the challenge of cholesterol to the periphery, the greater is the reverse cholesterol transport and other beneficial functions, and the lower is the risk of CAD events<sup>15</sup>. In our study, Apo B was found to be significantly high and Apo A1 was found to be significantly low in cases, as compared to control group (Table I).

LPI effectively incorporates this ratio into its formula and multiplies it with total cholesterol, triglyceride, and Lp(a) and forms a single composite index to assess risk of CAD. LPI was calculated in our study to produce a single cut-off point for predicting risk of CAD in diabetic patients with greater sensitivity and specificity than LTI. A similar study has been done in the past among adolescents and children<sup>3</sup> but no such study has been done in diabetic patients. LPI calculated in our study showed a sensitivity of 100% and specificity of 97.50% which is much higher than the specificity and sensitivity of LTI proving that LPI is a better indicator in calculating the risk of coronary artery disease in diabetic patients.

## Conclusion

Real burden of CAD is still unassessed by these 2 indices. But from our study, it is clear that non-conventional risk factors have a very important role in the epidemic of CAD in India. Both these indices are composite indices and include several non-conventional risk factors and LPI seems to be better.

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## Abdominal Tuberculosis: Diagnosis and Management in 2018

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### Abstract

**Abdominal tuberculosis is an important concern for clinicians in the tropical world. It is a great mimicker and the diagnosis is difficult due to low sensitivity of histological and microbiological tests. Response to therapy is often required for the diagnosis as a trial of antitubercular therapy is often resorted to in patients where diagnosis is uncertain. Appropriate definition of response is uncertain but mucosal healing (for intestinal tuberculosis) and ascites resolution (for peritoneal tuberculosis) can be used as objective criteria to define response. Six months of therapy is adequate for healing of the lesions but patients with intestinal tuberculosis may continue to be symptomatic due to persistent stricture and may warrant endoscopic dilatation or surgical intervention.**

**Key words:** Abdominal tuberculosis; intestinal tuberculosis; peritoneal tuberculosis; abdominal cocoon; PCR; granuloma; surgery.

Abdominal tuberculosis (ATB) is an important form of extrapulmonary tuberculosis which is often difficult to diagnose because of the low sensitivity of microbiological and histological testing<sup>1</sup>. The present review will focus on recent evidence for diagnosis and management of abdominal tuberculosis in the present era.

### Classification

ATB is classified into four major patterns of involvement: peritoneal, luminal, visceral or lymph nodal (Table I). Peritoneal tuberculosis is described as wet-ascitic type, dry-plastic type and fixed-fibrotic type<sup>2</sup>. However, in the literature the descriptions of the latter two variants, i.e., dry-plastic type and fixed-fibrotic type are often overlapping. Of late, a special variant of peritoneal tuberculosis, i.e., abdominal cocoon is also being recognised<sup>3,4</sup>. The luminal form of tuberculosis may be intestinal, oesophageal, gastroduodenal, etc. Visceral abdominal tuberculosis refers to involvement of organs like liver, spleen, pancreas, etc., while lymph nodal involvement of abdominal lymph nodes may be an isolated phenomenon or associated with other forms of abdominal TB<sup>1</sup>.

### Clinical features

The clinical features vary as per the site of involvement. Intestinal tuberculosis (ITB) may be associated with abdominal pain, episodes of intestinal obstruction, diarrhoea, weight loss and lack of appetite with fever. The symptoms may be related to the pattern of involvement. In predominant ulcerative form of morphological involvement, chronic diarrhoea may be a dominant feature while in hypertrophic (pseudotumoral) or stricturing forms,

abdominal pain and intestinal obstruction are usual manifestations<sup>5,6</sup>. Peritoneal tuberculosis is characterised by presence of abdominal pain (or discomfort), distension, fever and other constitutional symptoms. The dry-plastic and fixed-fibrotic forms may have more of abdominal pain and intestinal obstruction. Abdominal cocoon may present with pain, intestinal obstruction and lump<sup>2-4</sup>.

**Table I: Patterns of involvement in abdominal tuberculosis.**

Peritoneal	Wet-ascitic Dry-plastic Fixed-fibrotic Abdominal cocoon
Luminal	Intestinal Oesophageal Gastroduodenal Peri-anal
Visceral	Hepatic Splenic Pancreatic
Lymph nodal	Isolated lymph nodal Secondary (with intestinal or peritoneal)

### Radiology

The use of imaging modalities for diagnosis of ATB is of extreme importance as it may help in mapping the extent and site(s) of involvement and guide the acquisition of tissue for diagnosis. Abdominal ultrasonography, although operator dependent, may demonstrate ascites, lymphadenopathy,

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peritoneal and omental changes as also mural thickening of the bowel wall. The findings on computed tomography may include ascites, lymphadenopathy (with hypodense center, calcifications), peritoneal involvement (thickening, nodularity, enhancement), omental involvement (omental thickening, nodularity and masses), mural thickening (asymmetric, mural enhancement), strictures, etc<sup>7</sup>. Computed tomography may help in acquisition of tissue from lymph nodes. Computed tomography can help in the diagnosis of abdominal cocoon and can demonstrate the membranous sac around the bowel loops<sup>8</sup>. MR Enterography has also been shown to be of value and may reveal more strictures than a small bowel follow-through examination<sup>9</sup>. However, none of the imaging features can be considered as diagnostic of tuberculosis and imaging is useful primarily as an aid to achieve tissue diagnosis<sup>10</sup>.

## Histology

The typical histological findings in ITB are presence of caseating granulomas and acid-fast bacilli; however, these findings are infrequent (Table II). Presence of noncaseating granulomas, although more sensitive, has lesser specificity. Granulomas can also be seen in Crohn's disease which mimics ITB closely. Certain features like larger (> 400 µm) granulomas, confluent granulomas, submucosal location of the granulomas, > 4 locations of granulomas, multiple granulomas or caecal location are suggestive of ITB<sup>11</sup>. In a meta-analysis of histological findings, caseating necrosis was found to have a sensitivity of 21% and specificity of 100% for diagnosis of ITB. The presence of confluent granulomas (merging of the boundaries of the granulomas) had a sensitivity and specificity of 38% and 99% respectively. The presence of ulcer lined by epithelioid histiocytes was demonstrated to have a sensitivity of 41% and specificity of 94%<sup>12</sup>. Therefore, it is apparent that histological diagnosis is feasible only in a minority of the cases, and newer modalities for the diagnosis of ITB need to be explored.

## PCR for abdominal tuberculosis

Polymerase chain reaction testing using various primers for the diagnosis of tuberculosis is emerging as an important tool for the quick and reliable diagnosis of tuberculosis. However, the utility in diagnosis of various forms of ATB is compromised by the low sensitivity. In a pooled estimate of eight studies, the IS 6110 gene segment was reported to provide a sensitivity of 47% and specificity of 95% for discrimination of ITB from CD<sup>13</sup>. However, it is pertinent to note that some tubercular strains do not have this gene segment in their genome and are unlikely to be diagnosed<sup>14</sup>. Therefore, use of multiplex PCR which utilises multiple primers may be of value. Indeed, one report on use of multiplex PCR using 16SrRNA, IS 6110, and devR

primers was reported to have a high degree of sensitivity for the diagnosis of abdominal tuberculosis (87% for ITB and 76% for peritoneal TB)<sup>15</sup>. The findings, however, await validation and a comparative study in patients with diagnostic confusion with Crohn's disease and follow-up may further clarify the utility in clinical setting.

**Table II: Sensitivity of various modalities for diagnosis of abdominal tuberculosis<sup>36</sup>(#).**

	Intestinal tuberculosis	Peritoneal tuberculosis
Caseating granulomas	21% (15 - 40%)	–
Granuloma	30 - 82%	–
AFB positivity	6 - 20%	2.9%
AFB culture	6 - 54%	34.7%
TB PCR	47% (20 - 87*%)	48 - 75*%
Gene Xpert	8%	18 - 19%
Ascitic fluid ADA (> 30)	–	94%
Laparoscopic visualisation and histology	–	92% and 93%

\* High sensitivity reported with multiplex PCR (3 primers)  
# Modified from Medicine update, 2016

## Gene Xpert

Xpert Mtb/Rif has emerged as an important tool for the diagnosis of pulmonary and lymph nodal tuberculosis. Some studies have evaluated the use of Xpert Mtb in abdominal tuberculosis. In one report from Delhi, among patients with intestinal tuberculosis the sensitivity for diagnosis of intestinal tuberculosis was reported to be low, and only 3 of the 37 (8%) patients had a positive Xpert<sup>16</sup>. In peritoneal tuberculosis two reports suggest that the sensitivity of Xpert is low: 12 of 67 suspected cases (17.9%) in one series and 4 of 21 (19%) cases in another series were positive for Xpert<sup>17,18</sup>. While it may also be helpful in guiding therapy for patients who have not responded to ATT in order to differentiate between CD and drug-resistant TB, the sensitivity for diagnosis is low. Therefore new tools and discovery of new biomarkers for rapid diagnosis of abdominal TB is one of the unmet needs in the management of this condition.

## Differentiation from Crohn's disease

The resemblance between Crohn's disease (CD) and tuberculosis has been documented as early as 1913<sup>19</sup>. While tuberculosis is endemic in India, the incidence of CD has also been increasing in the developing countries<sup>20,21</sup>. The diagnostic dilemma presents a challenge as the treatment



protocol for management of CD involves immunosuppressive agents. Thus, current Asia – Pacific guidelines recommend 8 - 12 weeks of empirical ATT in patients with diagnostic uncertainty<sup>22</sup>. A study which used a Bayesian model attempted to estimate the likelihood of ITB versus CD, calibrated to the local prevalence of tuberculosis. Certain findings favouring the diagnosis of CD included male gender, bloody stools, presence of perianal disease or features of intestinal obstruction, extraintestinal manifestations; colonoscopic findings of linear ulcers, cobblestoning, luminal stricture, mucosal bridging, and involvement of the rectum histopathological features like focally enhanced colitis; and computed tomographic findings of asymmetrical mural thickening, mural stratification, comb sign, and fibrofatty proliferation. The findings which seemed to favour the diagnosis of ITB included pyrexia, night sweats, pulmonary involvement, and peritoneal involvement in the form of ascites; endoscopic findings of transverse ulcers, ileocecal valve involvement and involvement of the caecum; histology showing confluent or submucosal granulomas, and ulcers lined by histiocytes; short segmental involvement on CT and a positive interferon- $\gamma$  release assay. This model was validated prospectively for the diagnosis of tuberculosis in a cohort of 49 patients (27 CD, 22 ITB) and demonstrated a sensitivity and specificity of 90.9% and 92.6%, respectively<sup>23</sup>. Further, in patients with diagnostic dilemma, ATT trial can be initiated and mucosal healing may be sought. In patients with evidence of ulcer healing at 2 months (early mucosal response) or at end of therapy, a confirmation of diagnosis is made or else an attempt is made to exclude drug-resistant tuberculosis or Crohn's disease<sup>24,25</sup>. CRP levels may also be used to follow-up these patients and mirror the mucosal healing in patients with suspected abdominal tuberculosis<sup>26</sup>.

### Tubercular abdominal cocoon

Abdominal cocoon, also known as sclerosing encapsulating peritonitis, is a rather rare entity, which usually presents as abdominal pain, lump or intestinal obstruction. Underlying pathophysiology is usually related to formation of a membranous sac around the small bowel loops<sup>27,28</sup>. Tuberculous abdominal cocoon (TAC) is established by the demonstration of a membrane around a part or whole of small intestine as visualised on computed tomography or magnetic resonance imaging or detected on surgery. Partial cocoon encases the small intestine while a complete cocoon also contains large intestine or other organs inside it<sup>3,4</sup>. The diagnosis of TAC can be established using Sharma, Singh and Mandavdhare's criteria for TAC<sup>3</sup>:

- a) Definite: patient of abdominal cocoon with definite tuberculosis (Microbiological evidence: bacteriologically confirmed-culture, smear, PCR

positivity) or histology (caseating granulomas).

- b) Clinically diagnosed case: clinical and radiological evidence, corroboratory evidence on histology-granulomas, biochemistry (elevated ADA) or skin test and exclusion of other diagnosis.

Treatment comprises use of effective ATT and conservative management of episodes of intestinal obstruction as the first-line of management. Surgical intervention with resection of membrane and adhesiolysis is reserved only for non-responsive cases<sup>4</sup>.

### Treatment of abdominal tuberculosis

Six-month treatment consisting of rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampicin, isoniazid and ethambutol for 4 months is recommended as per accepted guidelines<sup>29</sup>. Many physicians however tend to treat such patients for a longer time. Prolonged treatment is associated with poor compliance and increased risk of side-effects of potentially toxic drugs and should be avoided. A Cochrane review which included three RCT's and included 328 participants analysed six months of ATT vs longer treatment in the management of abdominal tuberculosis. It concluded that, with regards to clinical cure at the end of therapy and relapse of tuberculosis after drug withdrawal; a nine months course of ATT has no incremental benefit over six months therapy<sup>30</sup>.

Patients who were excluded from the review included HIV positive individuals, patients with co morbidities and those who were treated with ATT in the last five years. For the diagnosis of abdominal tuberculosis, all trials included in this review conducted endoscopic biopsies, histopathological correlation as well as AFB stain and culture of specimen. The RCT from India treated participants thrice weekly under a directly observed therapy programme, while treatment was given daily in the trial conducted in South Korea and also included ethambutol in the continuation phase<sup>31,32</sup>. Another Indian study compared six-months of ATT, given thrice weekly under DOTS, with a prolonged (nine-month) therapy administered daily<sup>33</sup>. The dosage of anti-tuberculous drugs was very similar in all three trials. A recent report detailing a real-world experience with 6 months of ATT also suggests adequacy of 6 months of therapy<sup>34</sup>. Some patients with adequate mucosal response (i.e., ulcer healing) with ATT continue to remain symptomatic due to intestinal strictures. In fact, only a quarter of the strictures improve with therapy and a majority of patients may continue to have abdominal pain<sup>35</sup>. Prolongation of ATT is unlikely to be of use in these patients who may benefit from endoscopic dilatation or surgical intervention.

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## When to Withdraw Anti Epileptic Drugs (AEDs)

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### Introduction

About 60 to 70% of patients with epilepsy experience a 5-year remission on antiepileptic drugs (AEDs)<sup>1,2</sup>. In a patient who is seizure-free, the issue arises whether AEDs are still needed. The decision to discontinue therapy in seizure-free patients is still a controversial matter. Moreover, there is no evidence that continued treatment ensures freedom from seizures. A population-based study of 144 patients followed-up for an average period of 37 years, showed that 67% were in remission, with or without therapy<sup>3</sup>. Another population-based study showed that 5-year terminal remission (off drugs) is about 50%, at 20 years after diagnosis<sup>4</sup>. Various other studies in untreated patients of epilepsy have shown that about 50% of patients remain seizure-free for more than 5 years<sup>5</sup>, and individuals with continued seizures decrease over time<sup>6</sup>.

### Why to consider withdrawal of anti epileptic drugs?

We have to consider withdrawal of AEDs because there is evidence of benefits of withdrawal on psychosocial well-being and economic burden of these patients.

#### A. Psychosocial factors

Taking AEDs on daily basis is, for patients, a regular reminder that they have a disease that may recur any time. The responsibility of remembering to take medicines, on time, can be regarded as an unwanted element in their daily lives. For patients with epilepsy, being seizure-free without AEDs is the only evidence that their disease is cured. Moreover, AEDs have cognitive side effects<sup>7,8</sup>. Several studies have shown better outcome on common neuropsychiatric and mood assessment scales, after AED withdrawal<sup>9-15</sup>.

#### B. Economic issues

As we know, the cost of AEDs is increasing day-by-day, so in suitable patients, it is quite reasonable to withdraw AEDs.

#### C. Adverse effects

Short-term and long-term adverse effects are very well

known with AEDs. Certain medications can cause undesirable side-effects like gum hypertrophy, hirsutism, and weight gain. Treatment with AEDs also has the risk of teratogenicity<sup>16</sup>. To a variable extent, all AEDs can cause sedation, ataxia, inattention and fatigue; adverse effects that have a negative impact on quality of life<sup>17</sup>. As older AEDs can induce and inhibit liver enzymes, they have risk of interaction with concurrent medications<sup>18</sup>.

#### D. Risk of recurrence of seizures after stopping AEDs

During or after withdrawal of AEDs, the relapse rate ranges from 12 - 62%<sup>19</sup>. A frequently cited study (MRC antiepileptic drug withdrawal group) in which patients who were randomised to continue treatment, showed a 22% relapse at 2 years while patients who were randomised to withdraw treatment, showed 41% relapse<sup>9</sup>. The meta-analysis of 25 studies by Berg and Shinnar, showed pooled relapse risk was 25% at 1 year and 29% at 2 years<sup>13</sup>. However, while interpreting the results of these studies, we have to see methodological issues as these studies enrolled heterogeneous group of patients.

#### E. Factors affecting the risk of relapse

Seizure control is better in idiopathic epilepsy than symptomatic epilepsy<sup>20,21</sup>. So, withdrawal of AEDs in individuals with symptomatic epilepsy is less successful than idiopathic epilepsy<sup>5,6,10,11,17</sup>. A study showed that relapse rate in cases of symptomatic epilepsy was 45%, as compared to 25% in patients with idiopathic epilepsy<sup>14</sup>.

There are some epilepsy syndromes which are associated with good outcome after AED withdrawal, like benign neonatal convulsions, benign childhood epilepsy with centrotemporal spikes and childhood absence epilepsy<sup>22,23</sup>.

In Juvenile myoclonic epilepsy (JME), the relapse rate is relatively high, therefore AED withdrawal is discouraged<sup>24</sup>. One unfavorable sign for AED withdrawal is multiple drug therapy, at the time of withdrawal<sup>9,10</sup>. Continuation of seizure activity, after starting of treatment, is another unfavourable sign for AED withdrawal.<sup>20</sup> Rate for success is proportional to the duration of seizure free period, before AED withdrawal<sup>9,15</sup>.

Age at the time of onset of seizure is an important risk

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factor in various studies. Seizure onset, before 10 - 12 years of age, is a favourable prognostic factor, while seizure onset after this age indicates a higher rate of relapse<sup>14</sup>.

The presence of neurologic deficits and mental retardation have been shown to be unfavourable factors in some studies<sup>19,20</sup>. These factors are usually associated with some underlying brain pathology which, in itself, carries relatively poor prognosis. According to some studies, the type of neurological deficit can be more important regarding this issue. For example the relapse rate was higher in patients of cerebral palsy with hemiplegia (62%) compared with patients of cerebral palsy with diplegia (14%)<sup>25</sup>. To be noted is that mental retardation is not a contraindication to AED withdrawal, as some studies have shown successful withdrawal<sup>26</sup>.

### Role of electroencephalography (EEG) in AED withdrawal

The role of EEG in withdrawal of AEDs is controversial. Many studies have shown that abnormal EEG before AED withdrawal has been a negative prognostic factor<sup>11,12,15</sup>, but the predictive value has not been confirmed<sup>15,16,27</sup>. There are many factors which account for limited predictive value of EEG. Epileptic discharges on EEG may be suppressed by medication in some patients which may give false negative results. The normalising effect of different AEDs differs to varying extent. Phenobarbitone, carbamazepine and phenytoin may affect the abnormalities on the EEG marginally, while sodium valproate have much more substantial effect. In some patients, EEG abnormality may not be seen until dose of AED is reduced that would have prognostic significance during AED withdrawal. In a study, relapse was seen in 83% of patients in whom EEG abnormality was seen during dose reduction, compared with a relapse rate of 54% of patients, in whom EEG abnormality not seen<sup>28</sup>. Other studies have also corroborated these findings<sup>29</sup>.

Another issue which affects the predictive value of EEG is limited sensitivity of EEG in epilepsy population, in general. A study conducted on US veterans population, with predominantly partial seizures showed abnormal EEG in 29% on initial recording. The yield increased to 59% after 3 or more EEGs<sup>25</sup>. The yield of EEG varies from 29 to 82% in various studies<sup>30,31</sup>. This limitation in EEG sensitivity affects its predictive value in choosing patients for withdrawal of AED. A normal EEG before AED discontinuation does not mean that outcome would be seizure-free, especially in the presence of other unfavourable factors.

Therefore, when we decide whether to withdraw AED, factors other than EEG need to be considered.

### Rate of AED withdrawal

In a cochrane review, outcomes of rapid versus slow withdrawal were assessed<sup>32</sup>. Only one study conducted on children satisfied selection criteria, showed no differences in relapse rate in rapid (6 weeks) versus slow (9 month) taper group.

### Relapse after AED discontinuation

In a review of 13 studies, seizure relapse rate after AED discontinuation varied from 12 to 66%<sup>33</sup>. In these cases, restarting of AEDs produced seizure remission in 64 - 91% cases after a mean follow-up period of 1 to 9 years. Poor prognostic factors for recurrences include symptomatic aetiology, cognitive impairment and partial epilepsy.

### Conclusion

Before discontinuation of AEDs, we have to assess carefully the risk-benefit ratio, as significant undesirable risk is involved. These risks include difficulties in predicting the outcome after stopping, frequent seizure recurrence and consequences of seizure recurrence. Therefore, before stopping AEDs patient should be counselled about risk of recurrence and consequences regarding driving and safety.

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## Post-Exposure Prophylaxis for HIV

*BB Rewari\*, SP Singh\*\*, Atul Kumar\*\*\**

### Introduction

Healthcare providers are prone to accidental exposure to blood and other body fluids or tissues, while performing their work duties.

Avoiding occupational exposure to blood and other body fluids is the primary way to prevent transmission of HIV, hepatitis B, hepatitis C and other blood borne pathogens, in healthcare settings. Post-exposure management protocols form an important element of work place safety. These guidelines describe the risks of infection, the preventive measures and the steps to follow after accidental occupational exposure.

The term “Healthcare personnel (HCP)” is defined as any persons, paid or unpaid; working in healthcare settings who are potentially exposed to infectious materials (e.g., blood, tissue, and specific body fluids and medical supplies, equipment, or environmental surfaces contaminated with these substances).

“Exposure” which may place an HCP at risk of blood-borne infection is defined as:

- A percutaneous injury (e.g., needle-stick or cut with a sharp instrument).
- Contact with the mucous membranes of the eye or mouth.
- Contact with non-intact skin (when the exposed skin is chapped or afflicted with dermatitis).
- Contact with intact skin, when the duration of contact is prolonged, with blood or other potentially infectious body fluids.

Post-exposure prophylaxis (PEP) refers to the comprehensive management instituted to minimise the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV, HCV). This includes first aid, counselling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person and depending on the risk assessment, the provision of short-term (4 weeks) of antiretroviral drugs, with follow-up and support, including maintaining confidentiality.

### Professions with higher chances of blood exposure:

- Nursing staff and students
- Emergency care providers
- Labour and delivery room personnel
- Surgeons and operation theatre staff
- Laboratory technicians
- Physicians

### Average risk of acquiring HIV, hepatitis B, hepatitis C after occupational exposure

The average risk of acquiring HIV infection after different types of occupational exposure is low, compared to the risk of acquiring infection with HBV or HCV. In terms of occupational exposure, the important routes are needle stick exposure (0.3% risk for HIV, 9 - 30% for HBV and 1 - 1.8% for HCV) and mucous membrane exposure (0.09% for HIV).

**Table I: Risk of exposure from different body fluids**

Exposure to body fluids considered ‘at risk’	Exposure to body fluids considered ‘not at risk’, unless these fluids contain visible blood
Blood	Tears
Semen	Sweat
Vaginal secretions	Urine and faeces
Cerebrospinal fluid	Saliva
Synovial, pleural, peritoneal, pericardial fluid	Sputum
Amniotic fluid	Vomit
Other body fluids contaminated with visible blood	

Fig. 1 and 2, below demonstrate common types of needlestick injuries and the activities associated with them.

### Practices that influence risk and how to reduce risk to occupational exposure

Certain work practices increase the risk of needle stick injury

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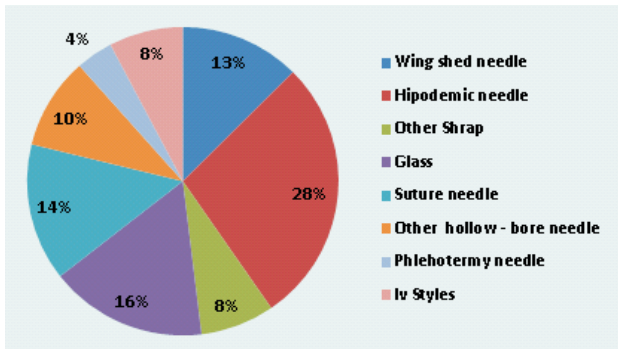


Fig. 1: How needle stick injuries occur.

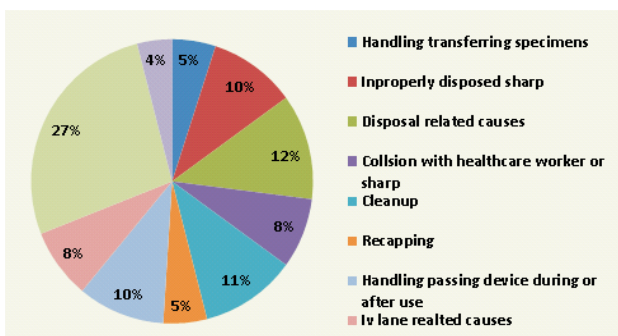


Fig. 2: Activities associated with needle stick injuries.

such as:

- Recapping needles (most important)
- Transferring a body fluid between containers
- Handling and passing needles or sharps after use
- Failing to dispose of used needles properly in puncture-resistant sharps containers
- Poor healthcare waste management practices

#### How to protect oneself from needle stick/sharps injuries:

- Strict compliance to universal work precautions
- Avoid the use of injections where safe and effective alternatives are available, e.g., oral drugs
- Avoid recapping needles
- Plan for safe handling and disposal of needles after use
- Promptly dispose of used needles in appropriate sharps disposal containers
- Report all needle stick and sharps-related injuries promptly to ensure that you:
  - Receive appropriate follow-up care
  - Participate in training related to infection prevention

- Use devices with safety features provided by the institute (wherever possible)
- Record and monitor injuries with an injury register in each location of healthcare setting.



Fig. 3: Do not recap needle.

#### Performing activities involving needles and sharps, in a rush increases the likelihood of an accidental exposure

**Minimise the use of sharps/injections:** All medical staff should try to minimise the use of invasive interventions for example – to use oral drugs in place of injections, wherever possible. Wherever the use of sharps is indicated, try to use safer alternatives, where practical and possible, within the limitations of the system.

**Protection against hepatitis B:** All healthcare providers (HCP) should be vaccinated against hepatitis B virus. The vaccination for hepatitis B consists of 3 doses: baseline, 1 month, and 6 months. Most (99%) seroconvert after completing the full course. There is no vaccine or prophylaxis against hepatitis C.

#### Table III: Universal precautions.

Universal precautions are intended to prevent the exposure of healthcare workers and patients to blood borne pathogens. These must be practiced in regard to the blood and body fluids of all patients, regardless of their infection status.

##### Universal precautions include:

- Hand-washing before and after all medical procedures
- Safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharp disposals; using needle cutter/destroyers; using forceps instead of fingers for guiding sutures; using vacutainers where possible
- Safe decontamination of instruments
- Use of protective barriers whenever indicated to prevent direct contact with blood and body fluid such as gloves, masks, goggles, aprons, and boots. A HCP who has a cut or abrasion should cover the wound, before providing care
- Safe disposal of contaminated waste

#### Management of the exposed person

##### Step 1: Management of exposure site – first aid

##### For skin – if the skin is pierced by a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin



Always use protective gear/Consider all blood samples as potentially infectious

Follow universal precautions practice-safe handling of sharp instruments-use needle destroyers

Fig. 1:

with water and soap and rinse

- Do not scrub
- Do not use antiseptics or skin washes
  - Don't use Bleach, chlorine, alcohol, betadine
- Do not put pricked/cut finger in the mouth: a childhood reflex
- After a splash of blood or body fluids:
- To unbroken skin:
  - Wash the area immediately
  - Do not use antiseptics
- For the eye:
  - Irrigate exposed eye immediately with water or normal saline
  - Sit in a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye
  - If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
  - Do not use soap or disinfectant on the eye
- For mouth:
  - Spit fluid out immediately
  - Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times
  - Do not use soap or disinfectant in the mouth
  - Consult the designated physician of the institution for management of the exposure immediately

### Step 2: Establish eligibility for PEP

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an Acidvidal exposure to blood (AEB). This evaluation must be made rapidly, so as to start any treatment as soon as possible after the accident.

This assessment must be made thoroughly (because not every AEB requires prophylactic treatment).

The first dose of PEP should be administered ideally within 2 hours (but certainly within the first 72 hours) of exposure and the risk evaluated as soon as possible.

Two main factors determine the risk of infection: the nature of exposure and the status of the source patient.

### Assessing the nature of exposure and risk of transmission

Three categories of occupational exposure for HCW can be described based on the amount of blood/fluid involved and the entry port. These categories are intended to help in assessing the severity of the exposure but may not cover all possibilities.

Table IV: Categories of exposures.

Category of exposure	Definition and example
Mild exposure (Exposure code 1)	Exposure to mucous membrane/non-intact skin with small volumes  E.g.: a superficial wound (erosion of the epidermis) with a plain or low calibre needle, or contact with the eyes or mucous membranes, subcutaneous injections following small-bore needles.
Moderate exposure (Exposure code 2)	Exposure to mucous membrane/non-intact skin with large volumes OR percutaneous superficial exposure with solid needle. E.g.: a cut or needle stick injury penetrating gloves.
Severe exposure (Exposure code 3)	Percutaneous exposure with large volume. e.g.: <ul style="list-style-type: none"> <li>● An accident with a high calibre needle (&gt; 18 G) visibly contaminated with blood</li> <li>● A deep wound (haemorrhagic wound and/or very painful); transmission of a significant volume of blood</li> <li>● an accident with material that has previously been used intravenously or intra-arterially</li> </ul>

The wearing of gloves during any of these accidents constitutes a protective factor. Note: In case of an AEB with material such as discarded sharps/needles, contaminated for over 48 hours, the risk of infection becomes negligible for HIV, but still remains significant for HBV. HBV survives longer than HIV outside the body.

### Assessing the HIV status of the source of exposure

A baseline rapid HIV testing of source of exposed should be done before starting PEP. Initiation of PEP where indicated should not be delayed while waiting for the results of HIV testing of the source of exposure. Informed consent should be obtained before testing of the source as per national HIV testing guidelines.



**Table V: Categories of situations depending on results of the source.**

Source code	Source HIV status	Definition of risk in source
–	HIV negative	Source is not HIV-infected but consider HBV and HCV.
1.	Low risk	HIV positive and clinically asymptomatic.
2.	High risk	HIV positive and clinically symptomatic.
	Unknown	Status of the patient is unknown, and neither the patient nor his/her blood is available for testing (e.g., injury during medical waste management, the source patient might be unknown).  The risk assessment will be based only upon the type of exposure and HIV prevalence in the area

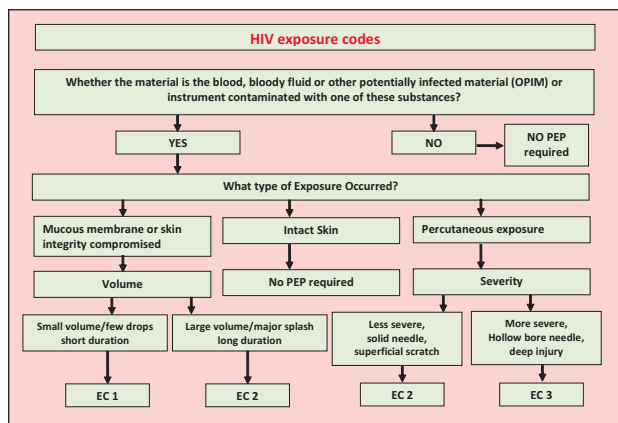
Routinely used HIV tests, do not detect HIV during the “window period”, as the antibody level is still too low for detection – but person can still have a high viral load. This implies that a positive HIV test result (of source) can help in taking the decision to start PEP, but a negative test result does not exclude HIV infection. In districts or some population groups with a high HIV prevalence, a higher proportion of HIV-infected individuals are found in the window period. In these situations, a negative result has even less value for decision-making on PEP.

**Step 4: Assessing need for PEP and prescribing PEP**

**Deciding on PEP regimen:**

The decision on need for PEP for HIV (following an occupational exposure in health care worker) will depend on the exposure as well as source person HIV status and extent of disease, if source is confirmed positive. It is decided based on exposure code and source code.

Depending on the exposure and source code, the decision to offer PEP, or defer it, should be considered, as shown in Table VI.



**Fig. 5: HIV exposure codes.**

**Table VI: NACO recommendations of PEP for HCP based on exposure and HIV source codes.**

Exposure code	Source code	Recommendation for PEP	Duration
1	1	Not warranted	–
1	2		
2	1	Recommended	28 days
2	2	PEP	
3	1 or 2		
2/3	Unknown	Consider PEP if HIV prevalence is high in given population and risk categorisation	28 days

In cases of sexual assault, PEP should be given to exposed person as a part of overall package of post-sexual assault care.

**What regimen to give for PEP**

**Table VII: Recommended PEP regimens.**

Dosages of the drugs for PEP for adults and adolescents		First dose	Second dose
Medication	3-drug regimen		
Tenofovir (TDF) Plus	300 mg once daily	Immediately within 2 hours of accidental exposure, either at day time or at night time	Next day at bed time with clear instruction to take it 2 - 3 hours after dinner and to avoid fatty food in dinner
Lamivudine (3TC) Plus	300 mg once daily		
Efavirenz (EFV)	600 mg once daily		

It is preferable to give these as fixed dose combination (single pill) wherever possible. Dual drug regimen should not be used any longer in any situation for PEP.

In case of intolerance to efavirenz, regimen containing tenofovir + lamivudine + PI (ATV/r or LPV/r) can be used after consulting an expert (experienced physician).

For persons already on ART, consult a specialist for decision on drug regimen to be used.

**Hepatitis B**

All health staff should be vaccinated against hepatitis B. The vaccination for hepatitis B consists of 3 doses: initial, 1 month, and 6 months. Sero-conversion after completing the full course is 99%.

If the exposed person is unvaccinated or unclear vaccination status give complete hepatitis B vaccine series.

**Table X: HBV vaccination after an AEB.**

HBV vaccination after an AEB	
HBV vaccination status of exposed person	Action after AEB
Never vaccinated	Give complete hepatitis B vaccine series
Vaccinated, anti-HBs not known	Give Hep B vaccine booster
Vaccinated more than 5 years ago	Give Hep B vaccine booster

*Note: If available, testing for the antibody level (anti-HBs) is not necessary. Hep B vaccine should be given as soon as possible after exposure. Do not wait for anti-HBs results, if test is done. Adequate levels of serum Ab to HbSAg (i.e., anti-HBs) is >10 IU/L.*

#### 7.4.10 Hepatitis C

There is presently no prophylaxis available against hepatitis C. There is no evidence that interferon, pegylated or not, with or without Ribavirin is more effective when given at this time than when given at the time of disease. Post-exposure management for HCV is based on early identification of chronic HCV disease and referral to a specialist for management.

#### Step 5: Laboratory evaluation

The reason for HIV testing soon after an occupational exposure is to establish a “baseline” against which to compare future test results. If the HCP is HIV-negative at the baseline test, it is in-principle possible to prove that subsequent infection identified by follow-up testing is related to the occupational exposure (depending on the timing of infection and consideration of other risks or exposures). When offered HIV testing, the exposed person should receive standard pre-test counselling according to the national HIV testing and counselling guidelines, and should give informed consent for testing. Confidentiality of the test result must be ensured.

**Do not delay PEP if HIV testing is not available.**

**Table XI: Recommended baseline laboratory investigations.**

Baseline laboratory investigations		
Timing	In person taking PEP (standard regimen)	In persons not taking PEP
<b>Baseline</b>	HIV, HCV, anti-HBs*, complete blood count, transaminases	HIV, HCV, anti-HBs*

\* HIV, HBV and HCV testing of exposed staff within 6 days of an AEB is recommended (baseline sero-status). Offer an HIV test in case of an AEB, as a positive HIV status may indicate the need to discontinue PEP. The decision on whether to test for HIV or not should be based on informed consent of the exposed person.

#### Step 6: Follow-up of an exposed person

Whether or not PEP prophylaxis has been started, follow-up is indicated to monitor for possible infections and provide psychological support.

**Clinical follow-up:** In addition, in the weeks following an AEB, the exposed person must be monitored for the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalised lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50 - 70% of individuals with an HIV primary (acute) infection and almost always within 3 to 6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART centre or for expert opinion should be arranged immediately.

Adherence and side-effect counselling should be provided and reinforced at every follow-up visit.

#### Clinical monitoring during PEP

- Monitor for acute sero-conversion illness
  - Within 3-6 weeks after exposure
  - If suspected, refer to ART centre
- Avoid:
  - Blood donation
  - Breast feeding
  - Pregnancy
- Person should use precautions:
  - Sexual relationship (Condom protection)
- Adherence and adverse drug reaction counselling

**Laboratory follow-up:** The exposed persons should have post-PEP follow-up HIV tests. Testing at the completion of PEP may give an initial indication of seroconversion outcome if the available antibody test is very sensitive. However, testing at 4 - 6 weeks may not be enough as use of PEP may prolong the time to seroconversion; and there is not enough time to diagnose all persons who seroconvert. Therefore, retesting at 3 months and again at 6 months is recommended.

**Table XII: Recommended follow-up laboratory monitoring (during and after PEP).**

Minimum laboratory follow up recommended for PEP for HIV*	
Timing	In person taking PEP (standard regimen)
Weeks 2 and 4	Complete blood count (for patients on AZT, this is particularly useful)
Week 6	HIV-Ab
Week 12 (month 3)	HIV-Ab
Week 24 (month 6)	HIV-Ab

\*It is important to remember that person exposed to risk of transmission of HIV is also having risk for getting infected with HBV and HCV and that also needs to be addressed

### Common side-effects of PEP drugs

Common side-effects of nucleoside/nucleotide analogues used for post-exposure prophylaxis include bone marrow suppression, nausea, vomiting, diarrhoea, abdominal pain, headache, myalgias, lassitude, malaise and insomnia.

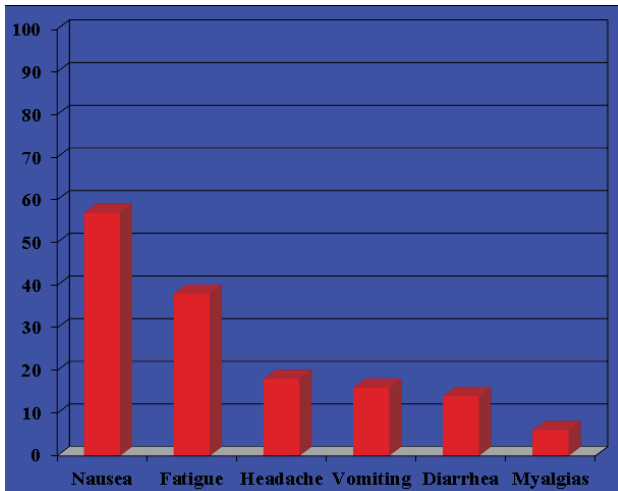


Fig. 7:

Addition of protease inhibitors to the post-exposure prophylaxis regimen is associated with increased side-effects noted for the nucleoside analogues, e.g., nausea, vomiting, diarrhoea, headache, abdominal pain) as well as anorexia, hyperlipidaemia, hyperglycaemia and worsening of pre-existing diabetes.

### Conclusions

Needle stick injuries are an important and continuing cause of exposure to serious and fatal diseases among HCP. It is important to educate HCP about various devices that can lead to injuries and various ways these injuries can occur. They must be educated about different ways and means, including Universal work precautions to minimise these risks. Also, it is very important for the HCP to be educated about timely reporting of the injury so that PEP measures can be instituted at earliest within the narrow time window available. A lot of work is going on to develop safer needle devices. We need greater collaborative efforts to accomplish a comprehensive programme that addresses institutional, behavioural and device-related factors to reduce needle stick injuries and development of infection related to them.

## Cystic Fibrosis Co-existing with Coeliac Disease: A Rare Case Report from India

Mohini\*, Varun Yadav\*\*, Nidhi\*\*\*, Aditi\*\*\*\*

### Abstract

*Cystic fibrosis is an autosomal recessive disorder. It has been rarely reported in India. The co-existence of cystic fibrosis (CF) and coeliac disease (CD) has been reported in various international studies.*

*Recently, we diagnosed a case of CF, with co-existing CD, in an Indian child. The patient was a boy with chronic productive cough since childhood with recurrent episodes of loose stools. Chest computed tomography showed diffuse bronchiectasis in both lungs. IgA-tTG was positive. Duodenal biopsy showed villous atrophy. Sweat chloride test was positive with level more than 60 meq/l. Genetic analysis revealed that he was compound heterozygote for D508, and also positive for HLA-DQ2.*

**Key words:** Cystic fibrosis, coeliac disease, bronchiectasis, IgA-tTG, sweat chloride test.

**Abbreviations:** CD, coeliac disease; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; EMA, antiendomysial antibody; HLA, human leukocyte antigen; Ig, immunoglobulin; tTG, tissue transglutaminase antibody; A/G, Albumin/Globulin.

### Introduction

Coeliac disease (CD) is a chronic autoimmune disease associated with intestinal malabsorption and has a genetic predisposition. Genetic linkage studies show a strong association with HLA-DQ genes<sup>1</sup>. The presence of genes coding for HLA-DQ2 and DQ8 explains upto 40% of the occurrence of CD in the European population. The diagnosis must be confirmed by a duodenal biopsy (classified according to Marsh criteria) which shows villous flattening, crypt cell hyperplasia and increased numbers of infiltrating intraepithelial lymphocytes<sup>2</sup>. Serological tests include transglutaminase-IgA (IgA-tTG) and endomysium-IgA (EMA) antibodies.

Cystic fibrosis (CF) is a common autosomal recessive genetic disease in the Caucasian population with an incidence of 1 in 2,500<sup>3</sup>. But, no such data is available for the Indian population. CF manifests in early childhood and is characterised by recurrent chest infections, recurrent sinusitis, bronchiectasis, chronic pancreatitis with pancreatic insufficiency, azoospermia and elevated sweat chloride level. The CFTR gene mutation leads to cystic fibrosis. This gene is located on the long arm of chromosome 7 and affects the salt and water movement across cell membranes. CFTR mutation analysis along with positive sweat chloride test is the cardinal test for diagnosis<sup>4</sup>. Sweat chloride level of 40 - 59 meq/l has been suggested to be normal. Presently, techniques used for confirming the

diagnosis of CF are gene mutation analysis, abnormal nasal potential difference and sweat chloride estimation. Infants with two CFTR mutations are considered to have CF while those with one CFTR mutation are referred for sweat testing to determine whether they have CF (sweat chloride > 60 meq/l) or are carriers (sweat chloride < 40 meq/l) only<sup>5</sup>. For patients in whom both the sweat test and mutation analysis are inconclusive, evidence of CFTR dysfunction is determined by abnormal nasal potential difference measurement<sup>6</sup>.

Clinical signs of CD are difficult to differentiate from CF with malabsorption, and patients may go undiagnosed for a long time. In a population where CD is common, we recommend screening for CD in patients with CF.

### Case summary

A 14-year-old boy presented with a history of high grade fever since 10 days, cough with purulent sputum production and breathlessness since 8 days. In addition, he had a history of recurrent productive cough and frequent foul smelling bulky stools, both since childhood. Expectoration was copious, thick, viscid and greenish in colour, more during early morning and lying down position and increased during exacerbations. The frequency of exacerbations was 1 - 2 times per year, initially, but now had increased to 4 - 5 times per year, since last two years. He was born prematurely at 32 weeks by normal vaginal delivery secondary to preterm

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labour with a low birth weight of 1900 gms. During development, he remained underweight and short stature according to his age. There was no history of childhood diarrhoea.

On general appearance, the patient was thin built and malnourished. His height was 125 cms and weight of 25 kgs with body mass index of 16.02 kg/m<sup>2</sup>. He was anaemic and grade 3 clubbing was present. Cyanosis, icterus and lymphadenopathy were absent. Patient was having dyspnoea with a respiratory rate of 45/min and heart rate of 104/min. His blood pressure was 100/66 mmHg. Post-nasal drip was noted. Oxygen saturation was 90%

on room air. Chest was bilaterally symmetrical with expansion of 2 - 3 cms. Intercostal recession and use of other accessory muscles of respiration was present. Percussion note was resonant bilaterally. On auscultation, both inspiratory and expiratory coarse crackles with occasional ronchi were present in all lung fields, more in infra-mammary areas. Rest of the systemic examination was normal. A diagnosis of CF with bilateral bronchiectasis, co-existing with CD was made on the basis of investigations (Table I and Table II). His family members were not evaluated by genetic mutational analysis, due to financial constraints.

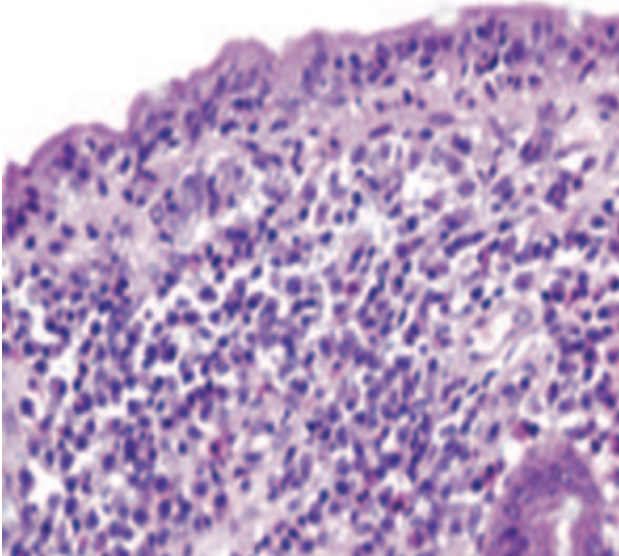
**Table I:**

Investigations	Normal values	Patient values	Comments
Haemoglobin	11 - 13 gm%	8.6 gm%	Anemia present
Total leucocyte count	4,000 - 11,000/cumm	18,000/cumm	Leucocytosis
Differential leucocyte count		P 90/I 08/M 01/E 01/B 0	Neutrophilic leucocytosis
Platelet count	1.4 - 4 lac/cumm	2.5 lac/cumm	Normal
Peripheral blood film	Normocytic normochromic	Microcytic hypochromic	Microcytic hypochromic anaemia
Random blood sugar	140 - 200 mg/dl	152 mg/dl	Normal
Blood urea	10 - 50 mg/dl	14 mg/dl	Normal
Serum creatinine	0.7 - 0.1.3 mg/dl	0.7 mg/dl	Normal
Serum sodium	135 - 145 mEq/l	140 mEq/l	Normal
Serum potassium	3.5 - 4.5 mEq/l	3.8 mEq/l	Normal
Total protein	6 - 8 g/dl	4.4 g/dl	Decreased
Albumin	3.5 - 5.5 g/dl	2.0 g/dl	Decreased
Globulin	2.5 - 3.5 g/dl	2.4 g/dl	Decreased
A/G	1 - 2	0.8	Decreased
Total bilirubin	0.2 - 0.8 mg/dl	0.5 mg/dl	Normal
Alkaline phosphatase	39 - 117 U/L	156 U/L	Increased
Urine complete exam	No albumin, no pus cells and no sugar detected	Normal report	Normal
Serum iron	50 - 150 µg/dl	28 µg/dl	Decreased (iron deficiency)
Serum ferritin	50 - 200 µg/l	18 µg/l	Decreased (iron deficiency)
Transferrin saturation	30 - 50%	26%	Decreased
Total iron binding capacity	300 - 360 µg/dl	402 µg/dl	Increased
Stool for ova/cyst and occult blood	Negative	Negative	Normal
Stool for fecal fat	Less than 7 g (in 24 hours)	6.1 gm	Normal
Serum IgA-tTG	< 5 U/ml	18.8 U/ml	Elevated (suggestive of coeliac disease)
Sputum examination		Positive for <i>Pseudomonas aeruginosa</i> and showed sensitivity to piperacillin-tazobactam and ceftazidime. Negative for AFB.	Suggestive of lower respiratory tract infection
Duodenal biopsy (Fig. 1)		Showed villous atrophy, crypt hyperplasia and lymphocytic infiltration	Suggestive of coeliac disease

**Table II:**

Investigations	Results	Comments
ECG	Normal study	No evident cardiac abnormality.
Echocardiogram	LV function – Normal, LVEF – 66 %, Valves – Normal, RA, RV – Mildly dilated	Suggestive of mild pulmonary hypertension
X-ray PNS	Bilateral maxillary and frontal sinuses appears to be normal	Normal X-ray PNS
Chest X-ray (Fig. 2)	Ring like and cystic opacities in Right upper, middle and lower zone and left upper and middle zones with low set and flattened domes of diaphragms, hyper inflated lung fields. Right pulmonary arteries are prominent.	S/o of bronchiectasis with emphysematous changes and normal cardiac size and silhouette.
CT chest	Extensive cystic and saccular bronchectatic changes involving both lungs, predominantly central (Right > Left) with complete collapse of Right middle lobe. Branching, nodular tree-in-bud opacities in periphery and both mid and lower lobes with no intra/inter lobular septal thickening.	Bilateral bronchiectasis of lungs Diagnostic of cystic fibrosis.
USG abdomen	Normal study	
CECT abdomen	Normal study	No evidence of chronic pancreatitis
Genetic analysis	Compound heterozygote of D508 and positive for HLA DQ2	Suggestive of cystic fibrosis and coeliac disease, both
Sweat chloride test	Positive, with level more than 60 meq/l	High sweat chloride confirms the diagnosis of CF. (Normal sweat chloride is 10 - 35 meq/l and always < 60 meq /l)

Patient was given supportive care, oxygen inhalation, routine nebulisation and intravenous antipseudomonal antibiotics for ten days. Gluten free diet was suggested to him. There was marked improvement in patient condition and patient was discharged after 1 week with prophylactic antibiotics, bronchodilators, mucolytics and regular follow-up was advised.



**Fig. 1:** Duodenal biopsy specimen showing villous atrophy and lymphocytic infiltrates.

## Discussion

Cystic fibrosis (CF) is a common inherited and clinically heterogeneous disorder that affects glands and secretory epithelia. Although more than 1,500 mutations are known to cause this disease, D508 and L997 are the main CF



**Fig. 2:** CXR – PA view showing bronchiectatic changes in RUZ, RMZ, RLZ, LUZ, and LMZ.

mutations known<sup>7</sup>. In India, the literature from very few studies reported DF508 mutation with a frequency of 19% - 44%<sup>7</sup>. Data about other gene mutations is not available in India as this disease has rarely been reported. It is difficult to identify patients having CD, in the CF population, because both CD and CF cause intestinal malabsorption in the majority of cases.

CF and CD, for many years were recognised as a single clinical entity. Sporadic case reports of co-existing CF and CD have been published since the 1960s. Rabinowitz reported the co-existence of CF with CD in a 42 year young obese patient, which is quite a rare entity<sup>8</sup>. Broekaert *et al* reported a higher prevalence of elevated CD serology in German CF patients (3.1% with elevated anti-tTG-IgA compared to 0.8% in the general population). The frequency of CD in this CF-population was 1.1%, which was reported higher than the general population of Germany. However, the frequency of HLA-DQ2 and -DQ8 was found similar to the general German population<sup>9</sup>.

Only gluten free diet can be used to manage coeliac disease and normalise gut functions. Standard of care for a patient of CF is intensive and includes periodic and chronic administration of oral and aerosolised antibiotics, bronchodilators, recombinant DNase aerosols, exogenous enzymes for pancreatic insufficiency, anti inflammatory medications and nutritional support. Chest physiotherapy, several times a day, promotes mucus clearance. Ivacaftor, an approved compound overcomes the G551D CFTR gating defect and can be used in patients with this genetic defect. Correction of the D508del processing abnormality (corrector molecules) is the new era of CF therapeutics under evaluation<sup>10</sup>.

## Conclusion

Clinical symptoms and signs of CD and CF, with malabsorption, are almost similar and very difficult to differentiate. The co-existence of CF and CD may have a

great impact on disease course, quality of life, and treatment outcome. Therefore, serological screening for CD should be included in the diagnostic work-up of CF patients with persistent gastrointestinal symptoms during the early course of disease. Furthermore, CF patients especially those with positive coeliac serology could be assessed for HLA-DQ2 and -DQ8 to assess those at risk for developing CD. In conclusion, CF might be a risk factor for CD despite a similar genetic predisposition compared to the general population.

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## Juvenile Systemic Lupus Erythematosus Presenting as Digital Gangrene

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### Abstract

*A 15-year-old female presented with dry gangrene of her fingers and toes with a history of multiple joint pains in both upper and lower limbs. Her work-up showed positive serology for Systemic Lupus Erythematosus (SLE). In SLE, such a case of digital gangrene as the initial presentation without secondary antiphospholipid syndrome has rarely been reported in the literature. Approximately 15 - 20% of patient with SLE will present in childhood and adolescence. As in adult onset SLE, approximately 80% of patients with childhood SLE are female. The earlier age of onset also correlates with a more severe disease, with early involvement of Kidney and nervous system which can contribute to a worse prognosis as well.*

**Key words:** Dry gangrene, secondary antiphospholipid syndrome, systemic lupus erythematosus.

### Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder affecting multiple organs and systems. Digital ulcers and gangrene are common skin manifestations of connective tissue diseases, especially systemic sclerosis, although they are relatively rare in SLE. The incidence of juvenile SLE is between 0.5 and 0.6 per 1,00,000<sup>1</sup>.

Digital gangrene in SLE is a rare form of vascular injury, and considered to be a severe complication of SLE, that generally leads to digital amputation. The aetiology of digital gangrene in SLE is complex. In this disorder; several factors, such as the presence of antiphospholipid antibodies, Raynaud's phenomena, overlap syndrome, atherosclerosis or vasculitis, are potential causes. The most likely cause may be a complication of antiphospholipid syndrome; however, there may be unidentified causes in addition to these conditions. This is a report of a young female who presented with digital gangrene in SLE; such presentation is rarely reported in the literature. There was no evidence of antiphospholipid antibodies and other potential factors in the present case. This form of gangrene is usually treated with glucocorticoids, anti-platelets, anticoagulation, and potent vasodilator agents.

### Case description

A 15 year girl presented with a history of multiple joint pains, intermittent episodes of fever since one year and blackening of left middle finger for last one month, with marked constitutional symptoms and decreased urine output for last one month. There was no pedal oedema or

any skin lesion. On examination, the middle finger of left hand was gangrenous. Later, her left fifth toe also became gangrenous and it progressed to all toes within 2 - 3 days and index finger of left hand also became involved (Fig. 1 and 2). All peripheral pulses were palpable and normal in volume. In her right foot, the tip of the fifth toe was cyanotic. In her left foot, the all toes were cyanotic and later became gangrenous. Other findings included mild swelling of knee, elbow and ankle joints. There were painful movements of



**Fig. 1:** Showing digital gangrene of index finger and amputated middle finger of left hand.

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**Fig. (b):** Showing digital gangrene of toes of bilateral feet.

small joints of hands as well. Blood pressure of patient was 130/76 mm of Hg, pulse rate 84/min and respiratory rate 16/min. All others systems were normal on examination.

**Laboratory findings:** Hb - 7 gm/dl, normocytic normochromic anaemia, TLC- 6,000/cmm, DLC (%) - 88/10/1/1, ESR-120 mm/h, CRP -28 mg/l, blood urea 113 mg/dl, S. Cr 0.9 mg/dl, serum calcium 7.8 mg/dl, serum proteins 6.3 gm/dl, A:G 0.5, serum triglyceride level 334 mg/dl, urine examination showed 3+ albuminuria, and 2.26 gm/day proteinuria on urinalysis. Immunologic studies revealed an ANA titer of > 1:40 (nuclear pattern), Ds-DNA titer of > 1,000 IU (< 30 IU), c-ANCA and p-ANCA negative, hypocomplementaemia was observed: C3 - 42.9 mg/dl (90 - 180 mg/dl), C4 - < 8 (10 - 40 mg/dl), anti U1RNP was 28.5 (< 20 units). Antiphospholipid antibodies, direct coomb's test, anti centromere antibody, anti scleroderma antibody, anti Smith antibody, anti La antibody, anti Ro antibody and rheumatoid factor were negative. A radiological work-up showed erosive changes in MCP joints of left hand and periarticular osteopenia. Electrocardiography showed non specific ST-T changes, echocardiography showed ejection fraction 46%, diastolic dysfunction with mitral regurgitation, with minimal pericardial effusion.

Patient was diagnosed as SLE with high disease activity, and initial treatment was started with, i.v., methyl prednisolone pulse therapy 750 mg per day for 3 days followed by oral prednisolone (1 mg/kg/day), inj. enoxaparin 40 mg BD followed by tablet acitrom 2 mg OD, aspirin (75 mg/day), hydroxychloroquine 200 mg BD, atorvastatin 10 mg OD, ramipril 2.5 mg OD, cilastazole 100 mg BD, tab mycophenolate mofetil 500 mg BD. For dry gangrene of

left middle finger, surgical amputation was done. The plan was to administer cyclophosphamide; however, the patient refused because she was worried about the side-effects of permanent ovarian failure. There was no improvement of gangrene although other symptoms, including musculoskeletal, improved after 16 weeks.

## Discussion

Systemic hypertension (44%) is the most common vascular manifestation of SLE followed by vasculitis (30%), Raynaud's phenomenon (26%), telangiectasia (20%), premature coronary atherosclerosis (6%), digital ulceration (6%), thrombophlebitis (6%), pulmonary hypertension (4%) and portal hypertension (4%). Diffuse systemic vasculitis similar to polyarteritis nodosa is rare (2%). Digital gangrene in SLE is a rare form of vascular injury and considered to be a severe complication of SLE that generally leads to digital amputation. The mechanisms include vasculitis, premature atherosclerosis, vasospasm, and hypercoagulability related to antiphospholipid antibodies. In general, anticoagulants, and low-dose aspirin are required to treat skin manifestations of SLE<sup>2</sup>. In our case, combined therapy was given to improve the symptoms. Although constitutional symptoms improved, there was no effective improvement in digital gangrene. In a study by Liu *et al*, among 18 lupus patients with digital gangrene, 15 patients received  $\geq 1$  mg/kg/day prednisone and all were treated with cyclophosphamide. Of these patients, eight cases failed and required digital amputation. This study concluded that prompt corticosteroid treatment (prednisone  $\geq 1$  mg/ kg/day started within 3 weeks) decreased the hazard of amputation,  $p = 0.073$ , HR = 0.13 (95% CI 0.01,1.21)<sup>3</sup>.

In conclusion, digital gangrene in SLE has rarely been reported especially in juvenile SLE. It responds poorly to treatment and carries worse prognosis because of multisystem involvement, especially kidney<sup>4</sup>.

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## Explosive Pleuritis: Presenting as a Life-Threatening Condition in a Young Adult

BD Sharma\*, Ashok Kumar\*\*, Vimal Nakra\*

### Abstract

*Explosive pleuritis is a very rare complication of streptococcal pneumonia. It presents as a rapidly progressive pleural collection, over a period of 24 hours involving 90% of the affected hemi-thorax, leading to respiratory distress and compromise of pulmonary function resulting into hypoxaemia. All the six cases which have been reported in the medical literature under this title have occurred in healthy young adult males in the age group of 30 - 50 years, with exudative, serosanguinous rapidly progressive, loculated, difficult to drain pleural effusions requiring ICD with pigtail catheter, use of fibrinolytic agents or Video Thoracoscopic Assisted Surgical drainage/decortications for urgent relief of acute respiratory distress. Group A Streptococcus has been the most community isolated organism from the pleural fluid in these patients. The pathogenesis of explosive pleuritis relates to the observation that streptococcal infections have a unique propensity to cause blockage of the peribronchial and subpleural lymphatics with cellular and necrotic debris. Purpose of reporting this case is to share our experience, as well increase awareness about this serious, and perhaps, grossly under reported clinical entity.*

**Key words:** Explosive pleuritis, fibrinolytics, video thoracoscopic assisted surgery.

### Introduction

Parapneumonic exudative effusions are seen in approximately 20 to 40% of patients hospitalised with pneumonia. These effusions generally resolve with treatment of the underlying pneumonia, very rarely evolving into empyaema. But it is the rapidity of progression from minimal to massive accumulation of pleural fluid in the affected hemithorax, leading to respiratory compromise and mediastinal shift to contralateral side, which make it life-threatening and hence the name 'Explosive Pleuritis'. The term explosive pleuritis was originally described by Braman and Donat<sup>1</sup> in 1986 as pleural effusions developing within hours of admission based on clinical, roentgenographic and microbiological evidence caused by group A beta-hemolytic streptococci, in the absence of bronchopneumonia. Subsequently, Sharma JK *et al*<sup>2</sup> defined explosive pleuritis as the rapid development of pleural effusion involving more than 90% of the hemithorax, within 24 hours. They postulated that the pathogenesis of explosive pleuritis relates to the observation that streptococcal infections have a unique propensity to cause blockage of the peribronchial and subpleural lymphatics with cellular and necrotic debris<sup>2</sup>. We present here one such case of explosive pleuritis in a 38-year-old healthy male who developed acute respiratory distress in spite of being on treatment in the hospital with appropriate antibiotics and other supportive measures. He required thoractomy and the use of urokinase to break the loculations for drainage, on an urgent basis for successful management.

### Case presentation

Mr A, a 38-year-old non-smoker, non-alcoholic, non-diabetic male presented to our hospital with history of high grade intermittent fever without chills or rigors for five days and pleuritic pain left lower chest for two days. He also had history of mild sore throat for last 2 days and progressively increasing dry cough for the initial two days of his illness. There was no history of expectoration/haemoptysis or shortness of breath, to start with. He was initially seen by his family physician who advised skiagram of the chest, complete blood count and started him on oral amoxicillin/clauvulanic acid and diclofenac with paracetamol for pain chest. Patient came to our hospital for lack of symptomatic improvement after two days of treatment. There was no past history of diabetes, hypertension, high-risk sexual behaviour, use of steroids or any immune-compromised status.

On examination at the time of presentation, patient was febrile, sick looking, conscious, oriented and communicative with BP - 130/80 mmHg, pulse - 116/min, regular and good volume. Respiratory rate 18/minute and SPO<sub>2</sub> of 96% on room air. Chest examination revealed normal vesicular breathing with decreased breath sounds in left lower chest. No pleural rub was heard. Cardiovascular system examination was essentially normal, other than sinus tachycardia. Abdomen was soft, nontender, no organomegaly and bowel sounds were normally heard. There was no focal neurological deficit or musculo-skeletal signs.

Investigations, from outside, showed haemoglobin of 15.1

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gm/dl, TLC - 20,300/cmm with 88% neutrophils, platelet count - 2,35,000/cmm, ESR - 55 mm 1st hour. Random blood sugar was 96 mg/dl. Skiagram of the chest showed an area of uniform haziness over the left lower zone with obliteration of left Costo-phrenic angle (Fig. 1). ECG showed sinus tachycardia. Liver and kidney functions tests were normal. Based on clinical and laboratory data a diagnosis of left pleural effusion was made and patient was started on Inj tazobactam 4.5 gm thrice daily, Inj clarithromycin 500 mg twice daily along with, Inj diclofenac and, Inj pantoprazole and other supportive treatment.

On day 2, ultrasound guided diagnostic pleural tap was done; pleural fluid was clear in appearance, pale yellow in colour with total protein - 6.2 gm/dl, albumin - 2.8 gm/dl and LDH - 969 IU. ADA was 23 IU. Pleural fluid cytology showed 750 cells/cumm with 85% neutrophils. Gram staining revealed gram positive cocci. Negative for malignant cells. No AFB were seen on Z-N stain.

However, patient became suddenly dyspneic, pain chest increased and oxygen saturation dropped to 84% on room air. ABG was suggestive of type 1 respiratory failure. He was put on oxygen support. Repeat ECG also showed only sinus tachycardia and 2D ECHO was normal with LV EF of ~ 55%. A repeat X-ray chest, done on urgent basis, showed markedly increased opacity in left hemi-thorax (Fig. 2). A working diagnosis of acute massive left pleural effusion was made. CT Chest was suggestive of gross left pleural effusion with collapse-consolidation of underlying lung with loculations (Fig. 3). Pulmonology consultation was sought and as per advice of pulmonologist inter-costal drainage (ICD) tube was put on urgent basis. But there was no output

from the tube and patient did not show any clinical improvement. Inj linezolid was added, in view of non responding pleural effusion with pleural fluid showing gram positive cocci.

On day 3, thoracic surgeon was consulted followed by thoracoscopy and adhesionolysis with Inj. urokinase 5,00,000 units given through ICD. Pleural biopsy done during the thoracoscopy revealed acute fibrinous tissue with acute inflammatory cells. Following this, output from the ICD started increasing, with 650 ml of drainage in next 24 hrs. Patient clinically became better, requirement for oxygen support decreased and TLC - decreased to 14,100/cmm. Blood, urine and pleural fluid cultures were sterile. Over the next 4 days, the drainage from the ICD



Fig. 2: Subsequent chest X-ray.



Fig. 1: Initial chest X-ray.

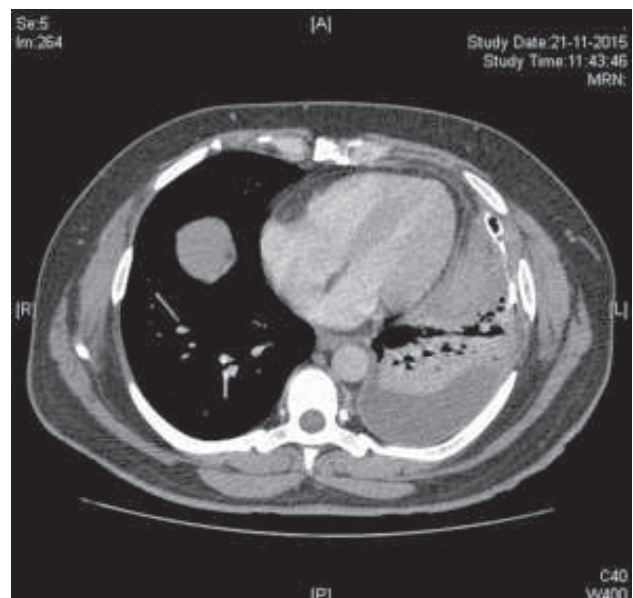


Fig. 3: CT scan of chest.

progressively decreased, patient improved clinically, TLC fell to normal range and repeat chest X-ray showed progressive clearing. Patient was discharged on day eight in fairly good condition, with final diagnosis of explosive pleurisy.

## Discussion

The acute and life-threatening presentation of rapidly progressive pleural effusion, as in our patient, has been described in anecdotal case reports in the medical literature as explosive pleuritis since 1986. The term 'Explosive pleuritis' was originally coined by Braman and Donat<sup>1</sup> in 1986 for pleural effusions developing within hours of admission. This definition was further refined by Sharma JK *et al*<sup>2</sup> for rapid development of pleural effusion involving more than 90% of the hemithorax within 24 hours, causing the compression of pulmonary tissue and a mediastinal shift to the contralateral side. Over the last 3 decades we came across only six cases<sup>1-6</sup>, published as case reports under the title explosive pleuritis. We feel that this condition is very much under reported.

**Table I: Common characteristics of reported cases of explosive pleuritis.**

Author	Age/sex	Pleural fluid	Organism isolated	Modality of treatment
1. Braman SS <sup>1</sup>	Young adult	Exudative	Group A streptococcus	ICD
2. Johnson JL <sup>3</sup>	29 male	Exudative/SS	Group A Streptococcus	ICD, Decortication
3. Sharma JK <sup>2</sup>	45 male	Exudative	Poly microbial growth	ICD, Decortication
4. Kumar SK <sup>4</sup>	31 male	Exudative/SS	Gram-positive Diplococci	ICD, Streptokinase
5. Al Mashat <sup>6</sup>	27 male	Exudative/SS	Group A Streptococcus	ICD, Decortication
6. Hatem N <sup>5</sup>	47 male	Exudative	Streptococcus intermedius	ICD, Fibrinolytics

SS: Sero Sangeinous.

Most of the reported cases presented with a dramatic clinical course, all in young adult males in the age group of 30 - 50 years, without any co-morbidities or predisposing factors for severe streptococcal infections, which is the predominant organism isolated from pleural fluid in these cases. There has, generally, been a history of preceding sore throat or upper respiratory infection, few days prior to the acute onset of high grade fever, pleuritic chest pain and respiratory distress, rapidly progressing on to hypoxaemia requiring emergency or MICU admissions and necessitating urgent thoraco-centesis for drainage of pleural fluid to

relieve the respiratory distress. Pleural fluid, in majority of cases, was sero-sanguinous in appearance and exudative in nature, showing gram positive cocci on gram staining and/or growing streptococci in pleural fluid culture. Ultrasonographic/CT examination of the chest almost invariably demonstrated fibrinous strands with loculations in the pleural collection, making it difficult to effectively drain sufficient fluid through the pigtail catheter (ICD) to provide symptomatic relief of the respiratory distress and improvement in hypoxaemia. After failure of ICD, many of these patients required individualised management with intrapleural injections of fibrinolytic agents like streptokinase or urokinase or video thoracoscope assisted surgical (VTAS) drainage or decortication for effective drainage of pleural fluid. In our patient, ICD through pigtail catheter did not succeed initially, but after intrapleural injection of urokinase, we could drain the pleural fluid effectively. Similar results have been reported by Kumar SK *et al*<sup>4</sup>, Hatem *et al*<sup>5</sup> and Maskell *et al*<sup>6</sup> in their cases. Pleural fluid cytology, in our patient, did show gram positive cocci, but it was sterile on culture, possibly due to prior use of antibiotics. As reported by Maskell *et al*<sup>7</sup>, more than 40% of patients with pleural effusion do not ever have a positive bacterial culture, and blood cultures are positive in only 12% cases of pleural infection.

Parapneumonic exudative effusions are seen in approximately 20 to 40% of patients hospitalised with pneumonia<sup>8</sup>. These effusions generally resolve with treatment of the underlying pneumonia, very rarely evolving into empyema. But if the rapidity of progression from minimal to massive accumulation of pleural fluid in the affected hemithorax leading to respiratory compromise and mediastinal shift to contralateral side earns it the name 'Explosive Pleuritis'.

An important feature of streptococcal pneumonia is the high frequency of pleurisy and pleural effusion that rapidly progresses to loculated empyema – so called "explosive pleuritis". This process can occur over a period of hours. Pathologically severe sero-sanguinous pleural effusion, haemorrhagic oedema of consolidated areas of the lung, and dilated lymphatics in the intralobular septa are present. Pleural effusions occur in 55 to 95% of patients with streptococcal pneumonia, with positive pleural fluid cultures in 30 to 40%<sup>3</sup>.

In a study of 434 patients with pleural infection by Maskell *et al*<sup>7</sup>, the most prevalent organisms cultured in community-acquired pleural infections were streptococcal species (*Streptococcus milliri* [32%], *Streptococcus pneumoniae* [13%], other *streptococci* [7%]) followed by anaerobes (16%) and *staphylococci* (11%).

The clinical presentation, physical signs and pleural fluid

findings in our patient were consistent with variable degrees of respiratory distress and respiratory system findings of large pleural effusion as described by other authors<sup>1-6</sup> in their patients of explosive pleuritis. The fluid drained in our patient was also sero-sanguinous and exudative. The diagnosis and treatment of this condition make thoracotomy essential. Thoracentesis alone may be ineffective. Although rapidly developing pleural effusions are best treated by early chest tube drainage because of a tendency towards early loculation, it is not unusual to have only minimal fluid drained from the pleural space with thoracocentesis<sup>9</sup>. In our patient also only a small amount of fluid could be aspirated initially. It was only after intrapleural urokinase injection that pigtail catheter drainage of the fluid could be completed over next 4 - 5 days.

Although in a randomised, controlled trial by Maskell *et al*<sup>10</sup>, intrapleural streptokinase was ineffective in reducing mortality, the need for surgical drainage, or the length of the hospital stay, other studies<sup>4,6,11</sup> as well as experience in our own patient suggest that fibrinolytic agents do lead to effective *in vivo* lysis of intrapleural fibrin adhesions and reduce the volume of infected pleural-fluid collections. Thus, there may still be a role for fibrinolytic agents in treating the small subgroup of patients who have an exceptionally large, loculated collection of pleural fluid that causes substantial dyspnea, hypoxaemia, or hypercapnia by the mechanical impairment of lung function early in their clinical course. With the early intrapleural injection of urokinase in our patient the pleural fluid drainage increased substantially and the patient had marked symptomatic relief from respiratory distress as well as improvement in hypoxaemia.

In view of the patient's rapid clinical deterioration and

progression of radiological findings characteristic of explosive pleuritis, this condition should be treated as a medical emergency and managed with intercostal drainage, intrapleural fibrinolytic agents or individualised surgical intervention, in addition to medical therapy with appropriate antibiotics and other supportive measures, as mandated by the clinical condition of the patient.

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## Oesophageal Cyst: A Rare Gastrointestinal Malformation

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### Abstract

*Oesophageal cyst is a rare gastrointestinal (GI) malformation which is diagnosed most commonly in childhood. In adults, it can present with a variety of common symptoms ranging from dysphagia, chest pain, epigastric discomfort, vomiting to more serious complications including infections, haemorrhage, and ulcerations. In our case, a young female presented with a short history of pain in abdomen and vomiting which turned out to be oesophageal cyst.*

**Key words:** Endoscopic ultrasound (EUS), fine needle aspiration (FNA).

### Introduction

Oesophageal cysts develop from aberrant elements of the oesophageal wall. Simple cysts are duplication of the epithelium, whereas true oesophageal cysts are duplications of the submucosa and the muscle wall.

Majority of these cysts are incidentally diagnosed in childhood and are asymptomatic but, when present in adults, they are more likely to be symptomatic<sup>1</sup>, depending on the location of the cyst. Wide range of symptoms from dysphagia, chest pain, epigastric discomfort, vomiting to stridor and non-productive cough have been reported. Right postero-inferior part of lower oesophagus is the most common site of occurrence where two-third of the cysts are diagnosed<sup>2</sup>. We herein report a case of a young adult presenting with upper abdominal pain that posed a diagnostic dilemma not only clinically but also on CECT chest as the lesion mimicked submucosal tumours like leiomyoma.

### Case report

A 28-year-old female presented with complaints of upper abdominal pain, since 1 week. To begin with, upper abdominal pain was colicky, associated with intake of solids and later to liquids as well, finally ending up in non-bilious, non-projectile vomiting, containing food particles and occurring within few minutes of a meal. There was no history of fever, haematemesis, loss of appetite, loss of weight, malena or any family history of malignancy.

Her physical examination was unremarkable with stable vitals. Systemic examination did not reveal any objective clue about her disease, except mild tenderness on deep palpation of epigastrium. Based on her clinical examination, a provisional diagnosis of acute gastritis was

made. Meanwhile, she was put on symptomatic treatment in the form of proton pump inhibitors. In spite of titrating symptomatic medications to maximum daily dosage, her condition did not improve and therefore, she was subjected to upper gastrointestinal endoscopy (UGIE) along with routine tests. Her routine blood tests, viz., complete haemogram, liver function test, kidney function test, urine and stool examination were normal, so was UGIE.

Since the patient did not improve a contrast enhanced computed tomography (CECT) of chest and abdomen was done. On CECT, a well defined elongated homogenous soft tissue lesion along right lateral distal thoracic oesophageal wall measuring 6.5 x 2.3 cm in size with no calcification and no scalloping of adjacent vertebral body was noted (Fig. 1) suggestive of leiomyoma.

To confirm the diagnosis, further investigation with Endoscopy guided ultrasound (EUS) and FNA was done which revealed a heteroechoic cystic lesion of size of 1.8 x 1.5 cm in distal oesophagus, arising from muscularis propria, extending about 5 cm in length without any breach in adventitia which was suggestive of true oesophageal



**Fig. 1:** CECT of chest.

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cyst. No mediastinal, celiac or subcarinal lymphadenopathy was observed. Nearly complete cystic fluid aspiration was done from 4 different sites and the samples were sent for cytological examination. Cytology consisted of lymphocytes and macrophages against a predominantly haemorrhagic background, without any granulomas, spindle cells or atypical cells suggestive of a benign oesophageal cyst. Patient improved symptomatically after diagnostic aspiration and she was discharged later in a stable condition.

## Discussion

Oesophageal cysts are rare and their true incidence is not yet well documented<sup>3,4</sup>. Upper abdominal pain is not a common symptom. Oesophageal cysts develop from aberrant elements of the oesophageal wall and usually do not communicate with the lumen of the oesophagus. Approximately 60% of oesophageal cysts develop in the lower third of the oesophagus, where difficulty in swallowing due to narrowing of lumen is the most common symptom. Twenty per cent occur in the upper third of the oesophagus with respiratory difficulty as the most common symptom because of compression of the tracheo-bronchial tree; and the remaining 20% occur in the middle-third of the oesophagus, where retrosternal chest pain and difficulty in swallowing are the most common symptoms. Posterior cysts in the lower-third of the oesophagus can cause cardiac arrhythmias because of irritation of the vagus nerve endings<sup>11</sup> (Fig. 3).

In the present case upper abdominal pain and vomiting without dysphagia (otherwise a common symptom of oesophageal cyst at this site) posed a diagnostic dilemma. CECT chest was also inconclusive. It was EUS which could

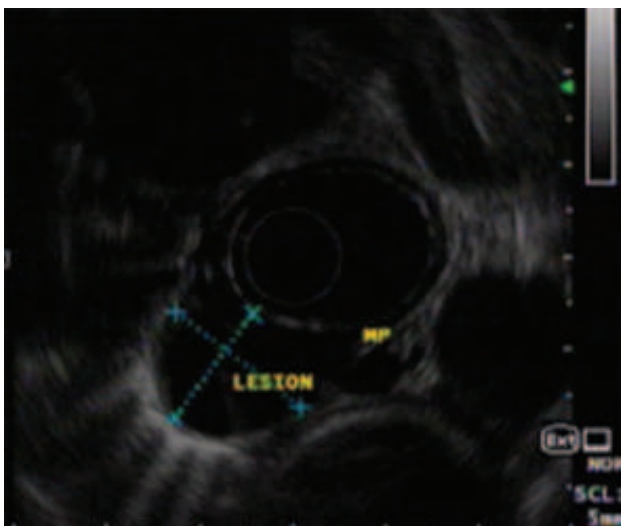


Fig. 2: Endoscopic ultrasound.

conclusively diagnose oesophageal cyst and has a therapeutic value, as well by relieving pain.

The cause of the unbearable abdominal pain was possibly due to involvement of sensory fibres of vagus nerve by progressive extra-luminal growth of oesophageal cyst simultaneously causing anti-peristalsis and vomiting. Since the growth was extra-luminal, dysphagia was not present.

Medical therapy has no role in the management of oesophageal cysts. All oesophageal cysts should be evaluated and, eventually, resected, except in those situations where the patient's other medical ailments prohibit surgery. Nearly 75% of patients with oesophageal cysts eventually become symptomatic, and need resection. Simple cysts are enucleated, whereas true duplication cysts are excised<sup>7</sup>. The future treatment of oesophageal cysts lies in the advancement of minimally invasive operative techniques, which will lessen morbidity and mortality. Endoscopic treatment has been reported as a feasible and reasonable alternative<sup>5</sup>. Robotic-assisted thoracic surgery has also been used for resection of an oesophageal cyst<sup>6</sup>.

In our case also, with the help of diagnostic EUS the cyst was nearly completely aspirated with relief of symptoms. Patient is under follow-up and there is no recurrence of symptoms, so far.

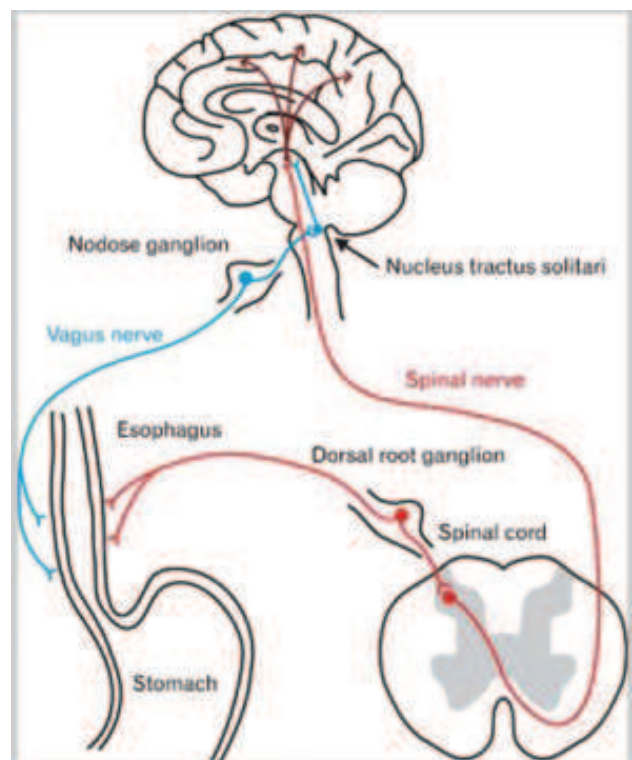


Fig. 3: Nerve supply of oesophagus.

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## An Interesting Case of Dapsone Hypersensitivity Syndrome

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### Abstract

**Background:** Dapsone is commonly used in many dermatological conditions. Dapsone hypersensitivity syndrome is a rare, potentially life-threatening adverse effect of dapsone with a characteristic triad of skin rash, fever and internal organ involvement.

**Case summary:** A 48-year-old female presented to emergency with complaints of fever, vomiting and rash all over the body. The erythematous papulovesicular rash started on the legs and forearms, progressing to involve the abdomen and face. Drug history revealed a recent prescription of dapsone, prescribed for oral lichen planus. Initial investigations revealed anaemia, leucocytosis, direct hyperbilirubinaemia, transaminitis, hypoalbuminaemia, deranged kidney function. The patient was administered IV steroids and she showed marked improvement.

**Conclusions:** Dapsone hypersensitivity syndrome is a rare reaction to a commonly prescribed drug. Recognition of this syndrome at the right time may prevent a potentially life-threatening outcome.

**Key words:** Dapsone syndrome, Dapsone hypersensitivity syndrome, Sulfone syndrome.

### Introduction

Dapsone or diaminodiphenyl sulfone is a drug commonly used in many dermatological conditions. It has many adverse effects like methaemoglobinaemia, haemolysis, nausea, vomiting, headache, and photo-sensitivity. Dapsone hypersensitivity syndrome or Dapsone syndrome or Sulfone syndrome is a rare, potentially life-threatening condition with a characteristic triad of skin rash, fever and internal organ involvement.

We present a 48-year-old female who was diagnosed by taking a thorough history and clinical examination supported by investigations and successfully treated.

### Case summary

A 48-year-old female presented to emergency with low grade fever, loose stools and vomiting for fifteen days and rashes on the upper and lower limbs, for the last three days which had spread to the abdomen and face. She conceded recent consumption of a drug prescribed by a dermatologist for her oral lesion, the name of which she could not remember. General examination revealed pallor, tachypnoea, tachycardia, white lacy patch in the oral cavity, and generalised oedema. An erythematous maculopapular rash was present over bilateral upper and lower limbs, abdomen and chest. Respiratory system examination was suggestive of a bilateral pleural effusion and abdominal examination revealed ascites. Initial investigations revealed Hb - 9.1 gm%, TLC -  $36.8 \times 10^9/l$ , neutrophils - 32%, lymphocytes - 55%, creatinine - 1.3

mg/dl, total bilirubin - 2.4 mg/dl, direct bilirubin - 1.2 mg/dl, albumin - 2.3 gm/dl, SGOT - 327 IU/L, SGPT - 679 IU/L, prothrombin time - 17.4s, INR - 1.56. Chest radiograph showed bilateral pleural effusion. Ultrasound and CT abdomen revealed hepatomegaly, mild splenomegaly, gall bladder wall oedema and ascites. The patient became severely dyspnoeic on the fourth day and was shifted to the ICU. On persistent prodding for drug history, the attendants brought a recent prescription of dapsone (100 mg at bed time for fifteen days), prescribed for oral lichen planus (which had been confirmed by biopsy); four weeks before the fever and six weeks before the rash. On the fifth day, investigations revealed a corrected reticulocyte count of 3.16%, LDH - 432 IU which suggested haemolysis, total and direct bilirubin of 2.7 mg/dl and 2.4 mg/dl respectively and SGOT - 972 IU/L, SGPT - 574 IU/L. The dermatologist reviewed the patient and a diagnosis of dapsone syndrome was made. The patient was administered IV steroids. She showed marked improvement, her kidney injury and liver injury resolved. She was discharged on the twelfth day with oral steroids, which were gradually tapered off in the OPD. The patient has been tapered off steroids and her rash has resolved completely.

### Discussion

Dapsone is a commonly prescribed drug in many dermatological conditions. In the Indian setting, leprosy is one of the common diseases for which dapsone is prescribed. Various adverse effects have been ascribed to

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dapsone therapy, which have been summarised in the Table below<sup>1</sup>:

System	Manifestations
Systemic	
● Dapsone syndrome	Dermatitis, Hepatitis
● DRESS syndrome	Dermatitis, Eosinophilia
● Nonspecific	Nausea, Headache, Dizziness, Fatigue
Haematological	Haemolytic Anaemia Methemoglobinaemia
Neurological	Peripheral Neuropathy
Dermatological	Stevens-Johnson syndrome Toxic epidermal necrolysis
Hepatic	Cholestasis, Hepatitis
Renal	Nephritis
Pulmonary	Pneumonitis, Pulmonary Infiltration with eosinophilia
Thyroid	Hypothyroidism

Dapsone syndrome is characterised by fever, skin lesions and internal organ involvement<sup>1</sup>. It can occur from a few



**Fig. 1:** Erythematous maculopapular rash seen on the face and chest.



**Fig. 2:** Erythematous maculopapular rash seen on the abdomen.

weeks to 6 months after the consumption of this drug. However, it commonly occurs around 5 - 6 weeks after the prescription and is hence sometimes called "five week dermatitis"<sup>2</sup>.

Dapsone syndrome is thought to occur due to production of toxic intermediate metabolites like nitrosamines<sup>3</sup>. It is a dose independent reaction that is thought to be predominantly a type IV hypersensitivity reaction but, could be a combination of type I, IV, III and Coomb's hypersensitivity reactions<sup>4</sup>.

Organ involvement may be in the form of pneumonia, hepatitis, carditis, nephrotic syndrome, renal papillary necrosis, and pancreatitis<sup>1,5</sup>. The patient may have haemolytic anaemia. Skin lesions may be in the form of vesicles, bullae, photosensitivity, maculopapular rash, eczematous lesions or exfoliative dermatitis<sup>1</sup>. Laboratory features may show haemolysis, anaemia, eosinophilia, lymphocytosis, hyperbilirubinaemia, transaminitis, hypoalbuminaemia<sup>6</sup> and hypergammaglobulinaemia<sup>1</sup>. The diagnosis of dapsone syndrome is a clinical one and patch test is an unreliable test<sup>2</sup>.

The differential diagnoses include DRESS syndrome, vasculitic syndromes, toxic epidermal necrolysis, Steven's Johnson syndrome, connective tissue disorders, viral infections, and rickettsial infections<sup>1,5</sup>. Most of these were systematically ruled-out in our case, and a rapid and significant response to steroids was a case in point.

The treatment of dapsone syndrome involves immediate discontinuation of dapsone, oral or IV steroids (dose of prednisolone 1 mg/kg/day or equivalent)<sup>1,5</sup>. The steroids should be tapered over a month. Mortality of 12 - 23% has been reported<sup>7</sup>, that can be prevented if treatment with steroids is initiated early.

## Conclusions

Dapsone hypersensitivity syndrome or dapsone syndrome is a rare hypersensitivity reaction to a commonly prescribed drug. A physician needs to be very vigilant about drug history in any patient with fever and rash. Recognition of this syndrome at the right time may prevent potentially life-threatening progression.

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## Fixed Drug Eruption Related to use of Fluoroquinolone and Nitroimidazole Combination in Ulcerative Colitis: Report of two Cases

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### Abstract

*Antibiotic use is common in the treatment of acute gastroenteritis and acute exacerbations of ulcerative colitis. Often a fixed drug combination of fluoroquinolones and nitroimidazole is used in such situations. We report two cases of fixed drug eruption (FDE) in patients with ulcerative colitis who received ornidazole with levofloxacin and ofloxacin, respectively. Herein, the drug used was a fixed dose combination of levofloxacin 250 mg and ornidazole 500 mg in the first case, and ofloxacin 200 mg and ornidazole 500 mg in the second case. In both the instances, the drug was used in the empirical therapy of an exacerbation of underlying ulcerative colitis. The first case was of a 38-year-old male who developed initial symptoms within an hour of intake of drug with itching and hyperpigmentation. The other patient was an 18-year-old male who developed skin lesions after two days (four doses) of the drug. Both patients improved with cessation of the drug. FDE with these agents has been reported only infrequently. The causality estimated for these cases was definite and probable for the first and second case, respectively.*

**Key points:** Fixed drug eruption, ulcerative colitis, nitroimidazole, fluoroquinolones.

### Introduction

Although guidelines recommend against it, the use of empirical antibiotics to treat exacerbations of ulcerative colitis is a common clinical practice<sup>1</sup>. This is in the belief that the exacerbations may be a result of superimposed bacterial or amoebic infection in patients with underlying ulcerative colitis. However, the use of antibiotics adds to the cost and may also lead to adverse effects. We report two cases of fixed drug eruption resulting from antibiotic use, for management of exacerbation of ulcerative colitis.

### Case reports

#### Case 1

A 38-year-old male was a known case of ulcerative colitis for 7 years and had evidence of extensive colitis, with a relapsing and remitting course. The patient was on mesalamine and folic acid, but developed bloody diarrhoea. Sigmoidoscopy revealed active disease in the form of active bleeding and superficial ulcerations. Stool workup for ova-cysts and *Clostridium difficile* toxin assay were negative. The patient had been prescribed an oral fixed dose combination of antibiotics (levofloxacin 250 mg and ornidazole 500 mg). But, the patient developed blackish discoloration at multiple places on his lips (Fig. 1) within 45 minutes of the ingestion of the first dose. The patient also recalled a previous similar episode with the use of ornidazole. The diagnosis of ornidazole related fixed drug

eruption was made and the fixed dose combination drug stopped. With stoppage of the drugs the blackish discoloration of the lip disappeared in four days without any treatment. The patient was given oral steroids for his active colitis which led to improvement. Presently, the patient is in remission on oral mesalamine. The score on Naranjo causality scale was 9, suggestive of a definite causation.



**Fig. 1:** FDE on the lips.

#### Case 2

An 18-year-old male was symptomatic for 2 months with

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increased stool frequency with passage of blood and mucus in the stools. He had received an oral fixed dose combination of ofloxacin 200 mg and ornidazole 500 mg, which resulted in blackish discoloration, associated with pruritus, over extensor side of the right forearm (Fig.2). The pruritus had started within two days of ingestion of the first dose (total four doses). The pruritus and blackish discoloration disappeared within five days of stoppage of the fixed dose combination drug, without any treatment. The patient underwent sigmoidoscopy, which suggested severe changes of colitis and biopsy revealed evidence of activity as well as chronicity in form of crypt abscess, crypt distortion and branching. The patient improved with initiation of oral mesalamine and is doing well. Contrary to the first case, this patient did not have any previous exposure history, so diagnosis of fixed drug eruption related to use of ofloxacin and/or ornidazole was established. The score on Naranjo causality scale was 6, suggestive of a probable causation.



**Fig. 2:** FDE on the forearm.

## Discussion

Fixed drug eruptions (FDE) is a common dermatological adverse drug reaction and accounts for 16 - 21% of all cutaneous drug reactions<sup>2</sup>. The exact mechanism is unclear, but the role of delayed classical type IV hypersensitivity reaction has been postulated. Morphologically, FDE is characterised by onset of round/oval, erythematous well-defined macules on the skin and/or mucosa. The lesions are normally asymptomatic, but they may be associated

with pruritus and burning sensation. FDE increase in number and severity on subsequent occasions. The lesions may be single or multiple and mostly affect the lips, genitalia and hands but may appear in any location<sup>3-5</sup>. FDE are a muco-cutaneous reaction to ingested drugs like cotrimoxazole, tetracycline, barbiturates, salicylates, ibuprofen, oxyphenbutazone, acyclovir, griesofulvin, tranexemic acid, and colchicine<sup>3,4</sup>. FDE associated with levofloxacin, ofloxacin and ornidazole have been reported<sup>3-10</sup>. Saha *et al*, in a hospital based observational study, found that the fixed dose combination of fluoroquinolones and nitroimidazole was the second most common cause of cutaneous adverse drug reaction was the FDE being the second most common manifestation<sup>11</sup>. Although all ages are vulnerable to FDE but the peak usually occurs at 21 - 40 years. Males have slightly higher predilection than female counterparts. Most FDE lesions tend to occur with oral route of administration. It mostly occurs in patients who intermittently receive the causative agent rather than on continuous administration. It also tends to occur in other drugs similar in structure to the causative agent (cross-sensitivity)<sup>6,8</sup>. Most of the times antibiotics are used irrationally in acute exacerbation of ulcerative colitis and acute gastroenteritis. This practice should be stopped, as judicious use of antibiotics can prevent this adverse drug reaction.

We did a Naranjo causality scoring, which suggested that the first case was definite and second was probable<sup>12</sup>; in both cases the adverse drug reaction was mild (level 2) according to modified Hartwing and Siegel scale<sup>13</sup> and definitely preventable according to modified Schumock and Thornton scale<sup>14</sup>. Both patients were advised against use of these antibiotics in future.

## Conclusion

Despite guidelines against it, fixed dose combinations of fluoroquinolones and nitroimidazole are often empirically used to treat acute exacerbations of ulcerative colitis and acute gastroenteritis. Judicious use of these antibiotics in this scenario as advocated. Those individuals who are known to be allergic to the constituents of the combination, or had skin eruption following consumption of the drug, should be warned against its future use.

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## DIAMICRON XR 60

## Kikuchi Fujimoto Disease: Clinicopathological Correlation

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### Abstract

*Kikuchi Fujimoto disease, also called as histiocytic necrotising lymphadenitis, is a rare, idiopathic self-limiting cause of lymphadenitis. It is most commonly seen in adult Asian females, younger than 40 years of age. The most common clinical manifestations of Kikuchi disease is cervical lymphadenopathy, with or without systemic signs and symptoms. We report a case of a 26-year-old female who presented with mildly tender cervical lymphadenopathy which on excision biopsy revealed necrotising granulomatous inflammation.*

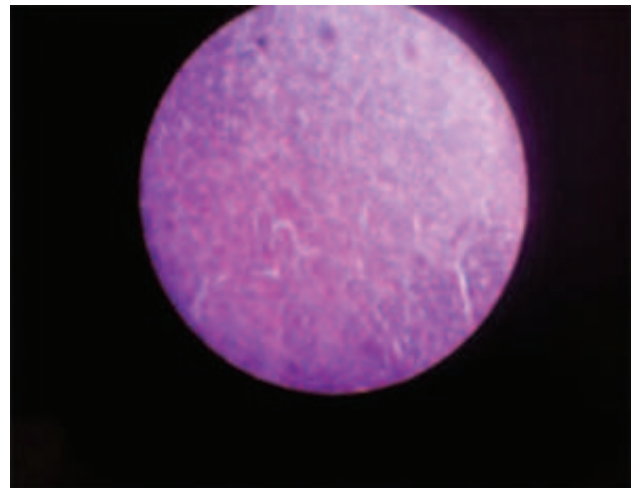
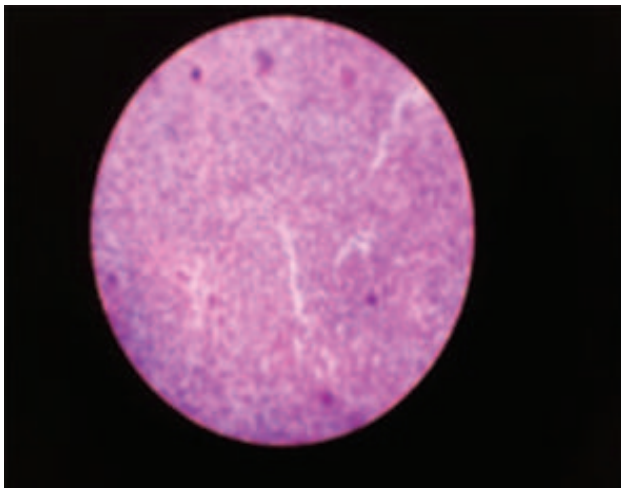
### Introduction

The disease was first described in the year 1972, in Japan by Kikuchi and later in the same year by Fujimoto and colleagues independently. Also known as histiocytic necrotising lymphadenitis, it is a rare, self-limiting disorder, typically affecting the cervical group of lymph nodes. Cases have been reported mainly from Japan with few cases from Europe and Asia, with a female preponderance. It affects mostly young adults of less than 30 years of age<sup>1-5</sup>.

### Case report

A 26-year-old female, known case of hypothyroidism, presented with multiple mildly tender cervical lymphadenopathy and malaise along with throat pain for 2 days. There was no history of fever/cough/night sweats/weight loss. Her vital parameters were within normal limits.

CBC, LFT, KFT and chest X-ray did not show any abnormality except for raised ESR (35). Patient was first started on antibiotics which gave no effective results. FNAC was done of the lymph nodes which was reported as reactive lymphadenitis favouring a diagnosis of tubercular lymphadenitis. Patient was started on antitubercular treatment which was stopped in 3 days as the patient reported increase in the size of the lymph nodes. Patient was then taken up for excision biopsy, which showed expansion of mantle zone with folliculolysis, foci of geographic necrosis seen with sheets of signet ring shaped histiocytes. No immunohistochemistry was done as no atypical lymphocytes were seen. A diagnosis of Kikuchi-Fujimoto's disease was offered. The biopsy material was sent for PCR which was negative for mycobacterium tuberculosis. Monospot test was negative (to rule-out infectious mononucleosis), HIV, ANA profile, anti ds DNA



**Fig. 1 and 2:** Cervical lymph node excision biopsy histopathological sections shows a fragmented lymph node showing expansion of mantle zone with folliculolysis. Foci of geographic necrosis is seen with sheets of signet shaped histiocytes.

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were found negative. The post-operative period was uneventful, and the patient was followed-up for next 3 months. She was treated conservatively with NSAIDs, antiemetics as per need. She was given corticosteroids, which is recommended but efficacy is uncertain. Patient recovered completely and was symptom free in the next 3 months.

## Discussion

Kikuchi-Fujimoto disease is an enigmatic, benign and self-limiting condition characterised by regional tender lymphadenopathy, predominantly including the cervical region, with or without fever and night sweats<sup>4</sup>. Lymphadenopathy may take several weeks to 6 months to resolve.

Described independently in 1972 by Kikuchi and Fujimoto *et al*, from Japan, till date most of the cases have been reported from East Asia, mostly affecting the younger population (20 - 30 years) with a female preponderance<sup>1-5</sup>. Of late few cases have been reported from the western countries.

The disease although is self-limiting, it can recur in about 3% of cases. Three deaths have been reported that occurred during the acute phase of generalised Kikuchi disease. One patient died from cardiac failure, second from effects of hepatic and pulmonary involvement, and the last from an acute lupus like syndrome. Another fatality has been reported in which Kikuchi disease appeared concurrently with SLE and was complicated with haemophagocytic syndrome and severe infection<sup>6</sup>.

The cause of Kikuchi disease is unknown, although infectious and autoimmune aetiologies have been proposed<sup>7</sup>. The most favoured theory proposes that Kikuchi disease results when one or more unidentified agents trigger a self-limited autoimmune process. Lymphadenitis results from apoptotic cell death induced by cytotoxic T lymphocytes. Some human leukocyte antigen (HLA) class II genes are more frequent in patients of Kikuchi disease, suggesting a genetic predisposition to the proposed autoimmune response. Features that support a role for an infectious agent include the generally self-limited course of the disease and its frequent association with symptoms similar to those of upper respiratory tract infection. Several viral candidates have been proposed, including, Cytomegalovirus, Epstein-Barr virus, Human herpes virus, Varicella-Zoster virus, Parainfluenza virus, Parvovirus B19 and Paramyxovirus<sup>8</sup>. However, serologic and molecular studies have failed to link Kikuchi disease to a specific pathogen, and more than one pathogen may be capable of triggering the characteristic hyperimmune reaction leading to Kikuchi

disease. The differential diagnosis of cervical lymphadenitis is huge but the principal conditions to be distinguished are lymphoma, metastatic tumour from local or distant site, drainage from infective lesions in dependent skin and systemic conditions such as infectious mononucleosis, HIV, and most commonly tuberculosis. There are several reports suggesting an association between Kikuchi's disease and SLE<sup>5</sup>. However, no convincing evidence is available to confirm such association.

The definitive diagnosis can be made on lymph node biopsy. Characteristic histopathological findings of KFD includes irregular central or paracortical areas of necrosis with abundant karyorrhectic debris. The nodal architecture can be distorted. Abundant histiocytes at the margin of the necrotic areas are seen. The karyorrhectic foci are formed by predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Plasma cells are either scarce or absent<sup>3</sup>. Importantly, atypia in the reactive immunoblastic component is not uncommon and can be mistaken for lymphoma. The typical immunophenotype consists predominantly of T cells, with few B cells. Histiocyte associated antigens like CD68, lysozyme, myeloperoxidase are expressed by the histiocytes<sup>3,4</sup>. Absence of significant number of plasma cells and/or hematoxylin bodies helps to distinguish Kikuchi disease from SLE.

Treatment of Kikuchi disease is generally supportive. NSAIDs may be used to alleviate lymph node tenderness and fever. The use of corticosteroids, such as prednisolone, has been recommended in several extranodal or generalised Kikuchi disease, and in cases of prolonged fever and annoying symptoms lasting more than 2 weeks despite NSAID therapy, as well as for recurrent disease. Indications for corticosteroids use include neurological involvement, hepatic involvement and severe lupus like syndrome<sup>9</sup>.

## Conclusion

Kikuchi Fujimoto's disease is an uncommon, perhaps underdiagnosed condition of unknown aetiology and excellent prognosis. Recognition of this condition is crucial as it may mimic tuberculous lymphadenitis, lymphoma, metastatic disease, or a local inflammatory/infective process. Awareness, not only by the clinicians but also the pathologists, may help prevent the misdiagnosis and overtreatment.

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## FLAVEDON MR

## **Hypokalaemic Periodic Paralysis: Rare Presentation of Hypothyroidism**

*Manoj Saluja\*, Yogesh Swami\*\*, Saurabh Chittora\*\*\*, Pavankumar Pyarsabadi\*\*, Hemant Vimlani\*\**

### **Introduction**

Hypokalaemic periodic paralysis is the most common periodic paralysis, a rare channelopathy manifested by episodic flaccid weakness secondary to abnormal sarcolemmal excitability. Hypokalaemic paralysis may be caused by a short-term shift of potassium into cells, seen in hypokalaemic periodic paralysis (caused by familial periodic paralysis or thyrotoxic periodic paralysis), or a larger deficit of potassium as a result of severe renal or gastrointestinal potassium loss.

Thyrotoxicosis is the most common cause of secondary hypokalaemic periodic paralysis. Recurrent hypokalaemic paralysis is an extremely unusual presentation of hypothyroidism. To the best of our knowledge, there are very few case reports of hypothyroidism associated with recurrent hypokalaemic paralysis<sup>1-3</sup>.

### **Case report**

A 45-year-old female presented with weakness of all four limbs and inability to walk for last one day. Patient also had history of similar episodes, 4 times in last one year. Each episode lasted for 2 to 5 days followed by spontaneous complete recovery without potassium supplement in any form except for one episode which required hospitalisation. It usually started with early morning weakness without any diurnal variation. There was no history suggestive of altered sensorium, convulsion, visual, respiratory, or bulbar weakness. She had no symptom suggestive of hypothyroidism. There is no history of hypertension, diabetes mellitus or ischaemic heart disease.

This time the patient had quadriparesis with hypotonia, diminished deep tendon reflexes except delayed relaxation of ankle jerks, flexor plantar response, and prominent neck muscle weakness. She had normal higher mental functions, without any cranial nerve and sensory involvement. Urinary bladder involvement was also present as patient was bed wetting. She was averagely built, without pallor or oedema. Her thyroid gland was not palpable. Other systemic examination, including chest and abdomen, was normal.

Laboratory investigations showed haemoglobin (11.6 gm/dl) ESR (16 mm/1st hour), low potassium (1.6 mmol/l), and

normal sodium (142 mmol/l) and high serum creatine phosphokinase (CPK) level (978 IU/L) and CK-NAC level (556 IU/L). Her electromyography and nerve conduction studies were normal. Thyroid function test revealed very low level of thyroxine (both T3 and T4) with high thyroid-stimulating hormone (TSH > 7 µIU/ml). Hypokalaemia persisted during the attack, ranging from 1.6 to 3.2 mmol/l. Hypokalaemic paralysis was diagnosed, based on clinical and biochemical parameters. No cause of secondary hypokalaemia could be detected. Normal serum magnesium (2.1 mg/dl) and urinary calcium excretion ruled-out the possibility of Gitelman's syndrome. Urine pH was normal. Ultrasonography of the abdomen demonstrated normal adrenal gland.

MRI brain and whole spine screening was also, done which was normal.

During the period of hospital stay, patient was treated with intravenous potassium (IV potassium chloride, initially 40 meq/l of normal saline through peripheral vein, at a rate of 20 meq/h and then as per potassium levels) for a week that led to clinical recovery and also biochemical improvement to some extent. After starting oral levothyroxine replacement, the patient continued with oral potassium replacement (oral potassium chloride solution 40 meq twice daily) for another 2 weeks after which she could be safely maintained with levothyroxine only. Hypokalaemic state persisted for 4 weeks after levothyroxine replacement, though the patient was clinically well. Subsequently, serum TSH became normal alongwith normal serum potassium level. With adequate control of hypothyroidism, the patient did not have to take potassium supplements and no further attack of acute flaccid weakness has been reported so far (for a period of 4 months during follow-up).

### **Discussion**

Periodic paralysis may be primary or secondary type. The paralytic attack can last from an hour to several days and weakness may be generalised or localised<sup>4</sup>. Disturbances of potassium equilibrium can produce a wide range of disorders including myopathy, marked muscle wasting, diminution of muscle tone, power, and reflexes<sup>5</sup>. Primary hypokalaemic periodic paralysis is autosomal dominant

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and is exacerbated by strenuous exercise, high carbohydrate diet, cold and excitement, which was not found in this case<sup>4</sup>. In the primary type, episodes of weakness recur frequently.

Many cases of secondary periodic hypokalaemic paralysis have been reported in association with gastroenteritis, diuretic abuse, renal tubular acidosis, Bartter syndrome, villous adenoma of colon, and hyperthyroidism<sup>6</sup>. There was no history of diarrhoea, vomiting, or diuretic abuse in the present case. The absence of polyuria, polydipsia, nausea, vomiting, constipation, hypochloraemia, and hyponatraemia ruled-out Bartter syndrome. Similarly, none of the clinical features of renal tubular acidosis like polyuria, polydipsia, acidotic breathing, rickets, and pathological fractures were present in this case<sup>7</sup>. Laboratory findings such as normal urinary pH and lack of hyperchloraemia during the episode of paralysis also excluded renal tubular acidosis. Characteristic features of hyperaldosteronism, like hypertension and polyuria, were absent with normal adrenal gland on USG of abdomen.

The levels of thyroid hormones and TSH values in this patient indicate severe deficiency of thyroxine. The persistent hypokalaemia during early periods of thyroxine replacement can be due to the fact that thyroxine in pharmacological doses can cause increased potassium excretion and water diuresis in patients with myxoedema during initial part of therapy. This may result in hypokalaemia, especially in a patient with malnutrition and low stores of total body potassium.

Hypokalaemic periodic paralysis though common among Indian population, varies greatly in disease spectrum and magnitude due to the heterogeneous aetiologies behind it. Two case series that studied hypokalaemic periodic

paralysis in tertiary care centers of India have observed that around 45% of all those patients had a secondary cause for their condition and this secondary group had more severe hypokalaemia that needed longer time to recover<sup>8,9</sup>. Thyrotoxicosis, renal tubular acidosis, and primary hyperaldosteronism were among the common conditions leading to hypokalaemic periodic paralysis, but very few cases of hypothyroidism have been found to be the aetiology behind it.

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## Lujan-Fryns Syndrome

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A 22-year-old boy, who was being treated in psychiatry for abnormal behaviour and delirium for the last two months, was referred to our department for opinion regarding hyperflexible joints. There was a history of talking irrelevantly, delusions and inappropriate smiling for three years. His relatives also told that there was gradual change in his voice over the last five years. He was born of a non-consanguineous marriage and attained his milestones normally. He started schooling at the age of six years but

was never good at studies. He was a school dropout and studied till seventh standard only. There was no history of similar complaints in any other sibling. On examination, he had asthenic habitus, long narrow face, bushy eyebrows, high arched palate, low set ears, small mandible and hyperflexible joints (Fig. 1 - 3). His arm span was 164 cm and height was 154 cm, ratio being 1.06. He also had scoliosis and pes cavus (Fig. 4). He had mild mental retardation, hypernasality and abnormal behavior. There was no evidence of ectopia lentis on slit lamp examination. Other systemic examination was essentially normal. X-ray of spine showed mild scoliosis (Fig. 5). Ultrasound



Fig. 1: High arched palate.



Fig. 3: Hyperflexible joints.



Fig. 2: Long face, small mandible with low set ears.



Fig. 4: Pes cavus.

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**Fig. 5:** X-ray spine showing mild scoliosis.

abdomen, echocardiography and MRI of head was normal. His karyotype was 45 XY and homocysteine level was normal. A diagnosis of Lujan-Fryns syndrome was made as he had marfanoid features along with mental retardation and behavioural problem. He was advised speech therapy and psychological counseling.

Lujan-Fryns syndrome (LFS) or X-linked mental retardation with marfanoid habitus syndrome was first described in 1984 and is characterised by marfanoid features, facial dysmorphism, mental retardation, and behavioural problems<sup>1,2</sup>. The facial features in LFS include narrow long face, maxillary hypoplasia, small mandible, long nose, low set ears, thin upper lip, receding chin and high arched palate<sup>3</sup>. The marfanoid features include tall stature with increased arm span, long slender fingers, hyper-extensible joints, long second toe and sandal grip. There is hypernasality, generalised hypotonia and some have cardiac defects. MRI brain showed agenesis of corpus callosum in few cases<sup>3</sup>. Ectopia lentis is not seen in LFS. They have mild-to-moderate mental retardation, behavioural problems include attention deficit, shyness and emotional instability. Few patients can have schizophrenia, frank psychosis and hallucinations. Differential diagnosis includes Fragile X syndrome, Klinefelter syndrome and homocystinuria. LFS is generally seen in males and has X-linked dominant inheritance. Mutation in MED12 gene is a commonly described genetic abnormality in these patients. There is no specific treatment available; psychological support and speech therapy is generally advised.

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